(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 481 614 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number : **91308791.2**

(22) Date of filing : **26.09.91**

(51) Int. Cl.[5] : **C07D 471/04,** A61K 31/505, // (C07D471/04, 239:00, 221:00)

(30) Priority : **01.10.90 US 590981**

(43) Date of publication of application : **22.04.92 Bulletin 92/17**

(84) Designated Contracting States : **AT BE CH DE DK ES FR GB IT LI LU NL SE**

(71) Applicant : **MERCK & CO. INC.**
126, East Lincoln Avenue P.O. Box 2000
Rahway New Jersey 07065-0900 (US)

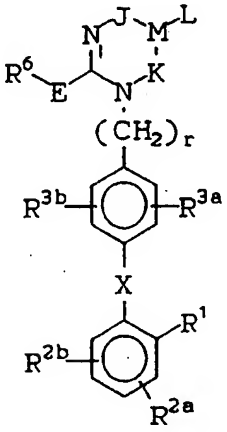
(72) Inventor : **Allen, Eric E.**
339 Hana Road
Edison, NJ 08817 (US)

Inventor : **Chakravarty, Prasun K.**
16 Churchill Road
Edison, NJ 08820 (US)
Inventor : **DeLaszlo, Stephen E.**
178 Monmouth Avenue
Atlantic Highlands, NJ 07716 (US)
Inventor : **Greenlee, William J.**
115 Herrick Avenue
Teaneck, NJ 07666 (US)
Inventor : **Patchett, Arthur A.**
1090 Minisink Way
Westfield, NJ 07090 (US)
Inventor : **Walsh, Thomas F.**
127 Marion Avenue
Westfield, NJ 07090 (US)

(74) Representative : **Barrett-Major, Julie Diane et al**
Merck & Co., Inc. European Patent Department Terlings Park Eastwick Road Harlow Essex CM20 2QR (GB)

(54) Substituted pyridopyrimidinones and related heterocycles as angiotensin II antagonists.

(57) Novel substituted pyridopyrimidinones of formula (I), which are useful as angiotensin II antagonists, are disclosed.



(I)

EP 0 481 614 A1

INTRODUCTION OF THE INVENTION

This invention relates to novel substituted pyridopyrimidinone and related heterocyclic compounds which are useful as angiotensin II antagonists in the treatment of elevated blood pressure and congestive heart failure. Thus, the substituted pyridopyrimidinone compounds of the invention are useful as antihypertensives.

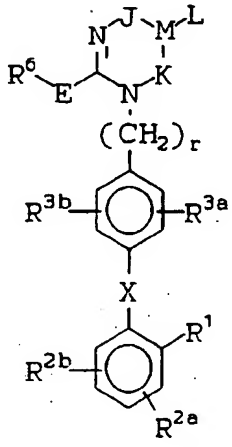
BACKGROUND OF THE INVENTION

Renin-angiotensin system (RAS) plays a central role in the regulation of normal blood pressure and seems to be critically involved in hypertension development and maintenance as well as congestive heart failure. Angiotensin II (AII), an octapeptide hormone is produced mainly in the blood during the cleavage of angiotensin I by angiotensin converting enzyme (ACE) localized on the endothelium of blood vessels of lung, kidney, and many other organs, and is the end product of the RAS. AII is a powerful arterial vasoconstricter that exerts its action by interacting with specific receptors present on cell membranes. One of the possible modes of controlling the RAS is angiotensin II receptor antagonism. Several peptide analogs of AII are known to inhibit the effect of this hormone by competitively blocking the receptors, but their experimental and clinical applications have been limited by their partial agonist activity and lack of oral absorption [M. Antonaccio. Clin. Exp. Hypertens. A4, 27-46 (1982); D. H. P. Streeten and G. H. Anderson, Jr. - Handbook of Hypertension, Clinical Pharmacology of Antihypertensive Drugs, ed. A. E. Doyle, Vol. 5, pp. 246-271, Elsevier Science Publisher, Amsterdam, The Netherlands, 1984].

Recently, several non-peptide compounds have been described as AII antagonists. Illustrative of such compounds are those disclosed in U.S. Patents 4,207,324; 4,340,598; 4,576,958; 4,582,847; and 4,880,804; in European Patent Applications 028,834; 245,637; 253,310; 291,969; 323,841; and 324,377; and in articles by A.T. Chiu, et al. [Eur. J. Pharm. Exp. Therap, 157, 13-21 (1988)] and by P.C. Wong, et al. [J. Pharm. Exp. Therap, 247, 1-7(1988), Hypertension, 13, 489-497 (1989)]. All of the U.S. Patents, European Patent Applications 028,834 and 253,310 and the two articles disclose substituted imidazole compounds which are generally bonded through a lower alkyl bridge to a substituted phenyl. European Patent Application 245,637 discloses derivatives of 4,5,6,7-tetrahydro-2H-imidazo[4,5-c]-pyridine-6-carboxylic acid and analogs thereof as antihypertensive agents.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to novel substituted pyridopyrimidinone and related heterocyclic compounds which are useful as angiotensin II antagonists, as antihypertensives, in the treatment of congestive heart failure, and in the treatment of elevated intraocular pressure. The compounds of this invention have the general formula (I):



(I)

wherein:

M is a C atom;

L is C or N when connected to K or J to form a ring as defined below;

J is -C(=Y)- where Y is 0 or NR^{21} and K and L are connected together to form a 6 membered aromatic ring containing one N atom that is not at K and five C atoms which may be substituted at the carbon atoms with R^7, R^{8a} and R^{8b};

K is -C(=Y)- where Y is 0 or NR^{21} and J and L are connected together to form a 6 membered aromatic ring containing one N atom that is not at J and five C atoms which may be substituted at the carbon atoms with R^7, R^{8a} and R^{8b} provided that only one of J or K is -C(=Y)-;

R^1 is

(a) $-CO_2R^4$,

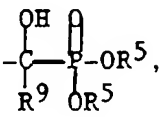
(b) $-SO_3R^5$,

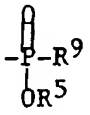
(c) $-NHSO_2CF_3$,

(d) $-PO(OR^5)_2$,

(e) $-SO_2-NH-R^9$,

(f) $-CONHOR^5$,

(g)  ,

(h) 

(i) $-SO_2NH$-heteroaryl as defined below,

(j) $-CH_2SO_2NH$-heteroaryl as defined below,

(k) $-SO_2NH-CO-R^{22}$,

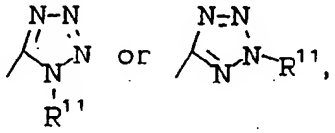
(l) $-CH_2SO_2NH-CO-R^{22}$,

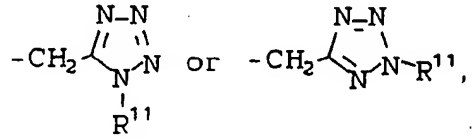
(m) $-CONH-SO_2R^{22}$,

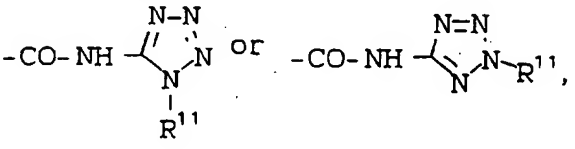
(n) $-CH_2CONH-SO_2R^{22}$,

(o) $-NHSO_2NHCO-R^{22}$,

(p) $-NHCONHSO_2-R^{22}$,

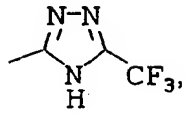
(q)  ,

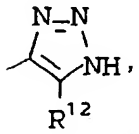
(r)  ,

(s)  ,

(t) $-CONHNHSO_2CF_3$,

(u) $-SO_2NH-CN$,

(v) 

(w) 

(x) - $PO(OR^5)(OR^4)$,

(y) - $SO_2NHCONR^4R^{22}$,

wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted five or six membered aromatic ring which can optionally contain from 1 to 3 heteroatoms selected from the group consisting of O, N or S and wherein the substituents are members selected from the group consisting of -OH, -SH, -C_1-C_4-alkyl, -C_1-C_4-alkoxy, -CF_3, halo (Cl, Br, F, I), -NO_2, -CO_2H, -CO_2-(C_1-C_4-alkyl), -NH_2, -NH(C_1-C_4-alkyl) and -N(C_1-C_4-alkyl)$_2$;

R^{2a} and R^{2b} are each independently

(a) H,
(b) halogen, (Cl, Br, I, F)
(c) NO_2,
(d) NH_2,
(e) C_1-C_4-alkylamino,
(f) di(C_1-C_4-alkyl)amino
(g) SO_2NHR^9,
(h) CF_3,
(i) C_1-C_6-alkyl,
(j) C_1 -C_6-alkoxy,
(k) C_1-C_6-alkyl-S-,
(l) C_2-C_6-alkenyl,
(m) C_2-C_6-alkynyl;
(n) aryl as defined below,
(o) aryl(C_1-C_4-alkyl),
(p) C_3-C_7-cycloalkyl;

R^{3a} is

(a) H,
(b) halo (Cl, Br, I, F)
(c) C_1-C_6-alkyl,
(d) C_1-C_6-alkoxy,
(e) C_1-C_6-alkoxyalkyl;

R^{3b} is

(a) H,
(b) halo (Cl, Br, I, F)
(c) NO_2,
(d) C_1-C_6-alkyl,
(e) C_1-C_6-acyloxy,
(f) C_3-C_7-cycloalkyl,
(g) C_1-C_6-alkoxy,
(h) -$NHSO_2R^4$,
(i) hydroxy(C_1-C_4-alkyl),
(j) aryl(C_1-C_4-alkyl),
(k) C_1-C_4-alkylthio,
(l) C_1-C_4-alkyl sulfinyl,
(m) C_1-C_4-alkyl sulfonyl,
(n) NH_2,
(o) C_1-C_4-alkylamino,

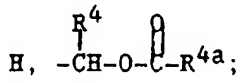
(p) di(C_1-C_4-alkyl)amino,
(q) fluoro-C_1-C_4-alkyl-,
(r) -SO_2-NHR^9,
(s) aryl as defined below,
(t) furyl,
(u) CF_3,
(v) C_2-C_6-alkenyl,
(w) C_2-C_6-alkynyl;

wherein aryl is phenyl or naphthyl optionally substituted with one or two substituents selected from the group consisting of halogen(Cl, Br, I, F), $N(R^4)_2$, CO_2R^4, C_1-C_4-alkyl, C_1-C_4-alkoxy, NO_2, CF_3, C_1-C_4-alkylthio, or OH;

R^4 is H, aryl as defined above or straight chain or branched C_1-C_6 alkyl optionally substituted with aryl or heteroaryl as defined above;

R^{4a} is aryl as defined above or straight chain or branched C_1-C_6-alkyl optionally substituted with aryl as defined above

R^5 is



E is a single bond, -$NR^{13}(CH_2)_s$-, -$S(O)_x(CH_2)_s$-where x is 0 to 2 and s is 0 to 5, -CH(OH)-, -O-, CO-;

R^6 is

(a) aryl as defined above optionally substituted with 1 or 2 substituents selected from the group consisting of halo (Cl, Br, I, F) -O-C_1-C_4-alkyl, C_1-C_4-alkyl, -NO_2, -CF_3, -$SO_2NR^9R^{10}$, -S-C_1-C_4-alkyl, -OH, -NH_2, C_3-C_7-cycloalkyl, C_3-C_{10}-alkenyl;

(b) straight chain or branched C_1-C_6-alkyl, C_2-C_5-alkenyl or C_2-C_5-alkynyl each of which can be optionally substituted with a substituent selected from the group consisting of aryl as defined above, C_3-C_7-cycloalkyl, halo (Cl, Br, I, F), CF_3, CF_2CF_3, -NH_2, -NH(C_1-C_4-alkyl), -OR^4 -N(C_1-C_4-alkyl)$_2$, -NH-SO_2R^4, -$COOR^4$, -SO_2NHR^9; or

(c) an unsubstituted, monosubstituted or disubstituted heteroaromatic 5 or 6 membered cyclic ring which can contain one to three members selected from the group consisting of N, O, S, and wherein the substituents are members selected from the group consisting of -OH, -SH, C_1-C_4-alkyl, C_1-C_4-alkoxy, -CF_3, halo (Cl, Br, I, F), or NO_2;
(d) C_3-C_7-cycloalkyl;
(e) perfluoro-C_1-C_4-alkyl,
(f) H;

R^7 is

(a) H,
(b) straight chain or branched C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,
(c) halo(Cl, Br, I, F) or
(d) CF_3;

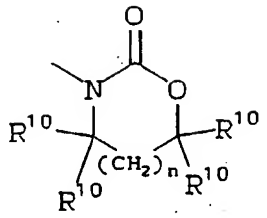
R^{8a} and R^{8b} are independently

(a) H,
(b) C_1-C_8-alkyl optionally substituted with a substituent selected from the group consisting of -OH, -guanidino, C_1-C_4-alkoxy, -$N(R^4)_2$, $COOR^4$, -$CON(R^4)_2$, -O-COR^4, -aryl, -heteroaryl, -$S(O)_x$-R^{22}, -tetrazol-5-yl, -$CONHSO_2R^{22}$, -SO_2NH-heteroaryl, -SO_2NHCOR^{22}, -$PO(OR^4)_2$, -$PO(OR^4)R^9$, -SO_2NH-CN, -$NR^{10}COOR^{22}$, -$(CH_2)_{1-4}R^4$,
(c) -CO-aryl,
(d) -C_3-C_7-cycloalkyl,
(e) halo (Cl, Br, I, F),
(f) -OH,
(g) -OR^{22},
(h) -C_1-C_4-perfluoroalkyl,
(i) -$S(O)_x$-R^{22},
(j) -$COOR^4$,
(k) -SO_3H,

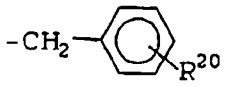
(l) $-NR^4R^{22}$,
(m) $-NR^4COR^{22}$,
(n) $-NR^4COOR^{22}$,
(o) $-SO_2NR^4R^9$,
(p) $-NO_2$,
(q) $-N(R^4)SO_2R^{22}$,
(r) $-NR^4CONR^4R^{22}$,

(s) $-OCNR^{22}R^9$,

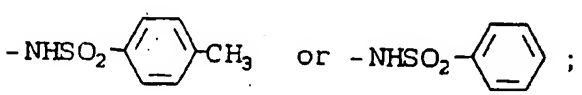
(t) -aryl or -heteroaryl as defined above,
(u) $-NHSO_2CF_3$,
(v) $-SO_2NH$-heteroaryl,
(w) $-SO_2NHCOR^{22}$,
(x) $-CONHSO_2R^{22}$,
(y) $-PO(OR^4)_2$,
(z) $-PO(OR^4)R^4$,
(aa) -tetrazol-5-yl,
(bb) -CONH(tetrazol-5-yl),
(cc) $-COR^4$,
(dd) $-SO_2NHCN$
(ee) $-NR^4SO_2NR^4R^{22}$,
(ff) $-NR^4SO_2OR^{22}$
(gg) $-CONR^4R^{22}$,
(hh)



where n=0 or 1.
R^9 is H, C_1-C_5-alkyl, aryl or arylmethyl;
R^{10} is H, C_1-C_4-alkyl;
R^{11} is H, C_1-C_6-alkyl, C_1-C_4-alkenyl, C_1-C_4-alkoxy alkyl, or



R^{12} is -CN, $-NO_2$ or $-CO_2R^4$;
R^{13} is H, (C_1-C_4-alkyl)CO-, C_1-C_6-alkyl, allyl, C_3-C_6-cycloalkyl, aryl or arylmethyl;
R^{14} is H, C_1-C_8-alkyl, C_1-C_8-perfluoroalkyl, C_3-C_6-cycloalkyl, aryl or arylmethyl;
R^{15} is H, C_1-C_6-alkyl;
R^{16} is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, aryl or arylmethyl;
R^{17} is $-NR^9R^{10}$, $-OR^{10}$, $-NHCONH_2$, $-NHCSNH_2$,

 ;

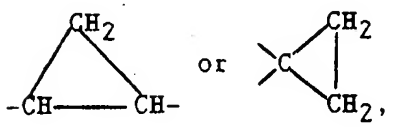
R^{18} and R^{19} are independently C_1-C_4-alkyl or taken together are $-(CH_2)_q-$ where q is 2 or 3;
R^{20} is H, $-NO_2$, $-NH_2$, -OH or $-OCH_3$;
R^{21} is
(a) aryl as defined above,
(b) heteroaryl as defined above,
(c) C_1-C_4-alkyl optionally substituted with a substituent selected from the group consisting of aryl as defined above, heteroaryl as defined above, -OH, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl$)_2$, $-CO_2R^{4a}$, halo(Cl, Br, F, I), $-CF_3$;
R^{22} is
(a) aryl as defined above,
(b) heteroaryl as defined above,
(c) C_3-C_7-cycloalkyl,
(d) C_1-C_6-alkyl optionally substituted with a substituent selected from the group consisting of aryl as defined above, heteroaryl as defined above, -OH, -SH, C_1-C_4-alkyl, $-O(C_1$-C_4-alkyl), $-S(C_1$-C_4-alkyl), $-CF_3$, halo (Cl, Br, F, I), $-NO_2$, $-CO_2H$, $CO_2-(C_1$-C_4-alkyl), $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl$)_2$, $-PO_3H_2$, $-PO(OH)(O-C_1$-C_4-alkyl), $-PO(OR^4)R^9$;
(e) perfluoro-C_1-C_4-alkyl;
X is
(a) a carbon-carbon single bond,
(b) -CO-,
(c) -O-,
(d) -S-,

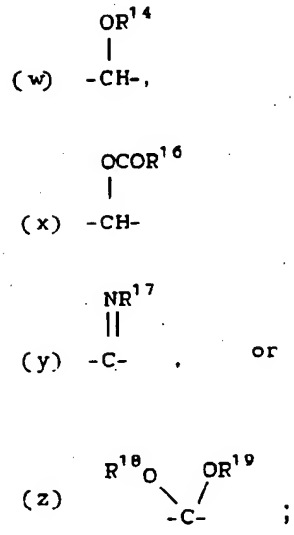
(e) $-\underset{\displaystyle R^{13}}{\overset{|}{N}}-$,

(f) $-CO\underset{\displaystyle R^{15}}{\overset{|}{N}}-$,

(g) $-NCO-$ (with R^{15} on N),

(h) $-OCH_2-$,
(i) $-CH_2O-$
(j) $-SCH_2-$,
(k) $-CH_2S-$,
(l) $-NHC(R^9)(R^{10})$,
(m) $-NR^9SO_2-$,
(n) $-SO_2NR^9-$,
(o) $-C(R^9)(R^{10})NH-$,
(p) -CH=CH-,
(q) -CF=CF-,
(r) -CH=CF-,
(s) -CF=CH-,
(t) $-CH_2CH_2-$,
(u) $-CF_2CF_2-$,

(v)  or ,



r is 1 or 2; and
the pharmaceutically acceptable salts thereof.

One embodiment of the compounds of formula (I) are those compounds wherein:

M is a C atom;

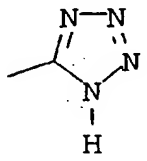
J is -C(O)-;

K and L are connected together to form a 6 membered aromatic ring containing one N atom that is not at K and five C atoms which may be substituted at the carbon atoms with R^7, R^{8a} and R^{8b};

R^1 is

(a) -COOH,

(b)



(c) $-NH-SO_2CF_3$;

(d) $-SO_2NH$-heteroaryl as defined above,

(e) $-CH_2SO_2NH$-heteroaryl as defined above,

(f) $-SO_2NH-CO-R^{22}$,

(g) $-CH_2SO_2NH-CO-R^{22}$,

(h) $-CONH-SO_2R^{22}$,

(i) $-CH_2CONH-SO_2R^{22}$,

(j) $-NHSO_2NHCO-R^{22}$,

(k) $-NHCONHSO_2-R^{22}$,

R^{2a} is H;

R^{2b} is H, F, Cl, CF_3, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, or aryl;

R^{3a} is H;

R^{3b} is H, F, Cl, CF_3, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_5-C_6-cycloalkyl, $-COOCH_3$, $-COOC_2H_5$, $-SO_2-CH_3$, NH_2, $-N(C_1-C_4\text{-alkyl})_2$ or $-NH-SO_2CH_3$;

E is a single bond, -O- or -S-;

R^6 is

(a) C_1-C_5 alkyl optionally substituted with a substituent selected from the group consisting of C_3-C_5-cycloalkyl, Cl, CF_3, CCl_3, $-O-CH_3$, $-OC_2H_5$, $-S-CH_3$, $-S-C_2H_5$, phenyl, or F;

(b) C_2-C_5-alkenyl or C_2-C_5-alkynyl; or,

(c) C_3-C_5-cycloalkyl;

R^7 is H;

R^{8a} and R^{8b} are independently

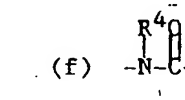
(a) H,

(b) C_1-C_8-alkyl optionally substituted with $COOR^{4a}$, $OCOR^{4a}$, OH, aryl, or $-(CH_2)_{1-4}R^4$;

(c) OR^{22},

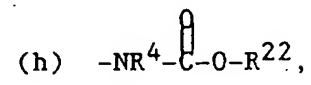
(d) -OH,

(e) $-NO_2$,



(f)

(g) $-CONR^4R^{22}$,



(h)

(i) $-NR^4R^{22}$,

(j) halo(Cl, F, Br),

(k) $-CF_3$,

(l) $-CO_2R^{4a}$,

(m) -CO-aryl as defined above,

(n) $-S(O)_x-R^{22}$,

(o) $-SO_2-NR^4R^9$,

(p) $-N(R^4)SO_2R^{22}$,

(q) aryl as defined above,

(r) $-NR^4CONR^4R^{22}$,

(s) $-N(R^4)SO_2N(R^4)R^{22}$;

X is a single bond;

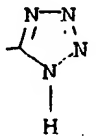
r is one.

In a class of this embodiment are those compounds of Formula (I) wherein:

R^1 is

(a) -COOH,

(b)



(c) $-NH-SO_2-CF_3$,

(d) $-SO_2NH$-heteroaryl as defined above.

(e) $-SO_2NH-CO-R^{22}$,

(f) $-CONH-SO_2R^{22}$.

E is a single bond;

r is one,

R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H, $-C_1$-C_6-alkyl, $-C_2$-C_6-alkenyl, $-C_2$-C_6-alkynyl, -Cl, -F, $-NO_2$, $-CF_3$;

R^6 is $-C_1$-C_4-alkyl, -cyclopropyl, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CF_3$, $-C_2$-C_5-alkenyl, -cyclopropylmethyl.

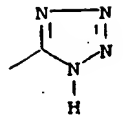
R^{8a} aid R^{8b} are each independently H, $-C_1$-C_4-alkyl, $-NO_2$, $-NR^4R^{22}$, $-OCH_3$, $-NR^4COOR^{22}$, -Cl, $-CH_2COOR^{4a}$, $-S(O)_x-R^{22}$ alkyl, $NR^4CONR^4R^{22}$, $CH_2OCO(C_1$-C_4- alkyl), NR^4COR^{22}, CO_2R^{4a}, -F, $-CH_2Ph$, $-CONR^4R^{22}$.

In a subclass are those compounds of Formula (I) wherein:

R^1 is

(a) COOH,

(b)



(c) $-SO_2NHCOR^{22}$,

(d) $-CONHSO_2R^{22}$,

(e) $-NHSO_2CF_3$;

R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H, $-C_1-C_4$-alkyl, -Cl or F;

R^6 is -n-propyl, ethyl, -n-butyl, -trans-2-butenyl, $CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$ -cyclopropyl, -cyclopropylmethyl;

R^{8a} and R^{8b} are each independently H, $-NO_2$, $-C_1-C_4$-alkyl, $-NH_2$, $-NHCOCH_3$, $-NHCH_3$, $-S(O)_x-R^{22}$, $-N(CH_3)_2$, $-OCH_3$, -COOH, $-COOCH_3$, $-CH_2OCOCH_3$, Cl, $-CH_2COOCH_3$, $-N(R^4)CON(R^4)_2$, $-N(R^4)CO_2R^4$, $-CH_2COOH$, $-N(R^4)COR^{22}$, $-OCH_3$, CH_2OH, NHMe, CH_2Ph.

Exemplifying this subclass are the following compounds:

(1) 2-n-Butyl-1l-[(2′-carboxybiphen-4-yl)-methyl]pyrido[2,3-d]pyrimidin-4(1H)-one;

(2) 2-n-Butyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrido[2,3-d]pyrimidin-4(1H)-one;

(3) 2-n-Butyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[3,2-d]pyrimidin-4(1H)-one;

(4) 2-n-Butyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[3,4-d]pyrimidin-4(1H)-one;

(5) 2-n-Butyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[4,3-d]pyrimidin-4-(1H)-one;

(6) 2-n-Butyl-6-methyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4-(1H)-one;

(7) 6-Amino-2-n-butyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4-(1H)-one;

(8) 2-n-Butyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl-8-methyl]pyrido[4,3-d]pyrimidin-4-(1H)-one;

(9) 2-n-Butyl-1-5-methyl-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[3,4-d]pyrimidin-4-(1H)-one;

(10) 2-n-Butyl-5,7-dimethyl-1-[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4(1H)-one;

(11) 6-Amino-2-n-butyl-5-methyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4(1H)-one;

(12) 2-n-Butyl-5-methyl-7-methylamino-1-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4-(1H)-one;

(13) 1-[(2′-(N-Benzoylsulfonamido)biphen-4-yl)-methyl]-2-n-butyl-5,7-dimethylpyrido[2,3-d]-pyrimidin-4-(1H)-one; and

(14) 2-n-Butyl-5,7-dimethyl-1-[(2′-(N-trifluoromethylsulfonylcarboxamido)biphen-4-yl)methyl]-pyrido[2,3-d]pyrimidin-4(1H)-one.

In a second embodiment are those compounds of formula (I) wherein:

M is a C atom;

K is -C(O)-;

J and L are connected together to form a 6 membered aromatic ring containing one N atom that is not at J and five C atoms which may be substituted at the carbon atoms with R^7, R^{8a} and R^{8b}. The class and subclass of this embodiment are the same as those described above.

Exemplifying this subclass are the following compounds:

(1) 2-n-Butyl-3-[(2′-carboxybiphen-4-yl)-methyl]pyrido[2,3-d]pyrimidin-4(3H)-one;

(2) 2-n-Butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrido[2,3-d]pyrimidin-4(3H)-one;

(3) 2-n-Butyl-3-[2′-(carboxybiphen-4-yl)-methyl]pyrido[3,2-d]pyrimidin-4(3H)-one;

(4) 2-n-Butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrido[4,3-d]pyrimidin-4(3H)-one;

(5) 2-n-Butyl-7-isopropyl-3-[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrido[4,3-d]pyrimidin-4-(3H)-one;

(6) 6-Amino-2-n-Butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4-(3H)-one;

(7) 6-Acetamido-2-n-Butyl-3-[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4(3H)-one;

(8) 2-n-Butyl-5-methyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[3,4-d]pyrimidin-4(3H)-one;

(9) 2-n-Butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl) methyl]-6-thiomethylpyrido[2,3-d]pyrimidin-4(3H)-one;

(10) 2-n-Butyl-7-carboxy-3-[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4-(3H)-one;

(11) 2-n-Butyl-7-(N-isopropylcarbamoyl)amino-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido-[3,2-d]pyrimidin-4-(3H)-one;

(12) 2-n-Butyl-6-(N-isobutyloxycarbonyl)amino-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido-[2,3-d]pyrimidin-4-(3H)-one;

(13) 2-n-Butyl-6-[N-(morpholin-4-yl)carbamoyl)-N-methyl]amino-3-[(2′-tetrazol-5-yl)biphen-4-yl)-methyl]-pyrido[2,3-d]pyrimidin-4(3H)-one;

(14) 2-n-Butyl-6-(N-isopropyloxycarbonyl-N-methyl)-amino-3-[(2′-tetrazol-5-yl)biphen-4-yl)methyl]-pyrido [2,3-d]pyrimidin-4(3H)-one;
(15) 6-(N-Benzyloxycarbonyl-N-methyl)amino-2-n-butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]-pyrido[2, 3-d]pyrimidin-4(3H)-one;
(16) 3-[(2′-(N-Benzoylsulfonamido)biphen-4-yl)]-methyl-2-n-butyl-6-(N-isopropyloxycarbonyl-N-benzyl) aminopyrido[2,3-d]pyrimidin-4(3H)-one;
(17) 2-n-Butyl-6-(N-isopropyloxycarbonyl-N-methyl)amino-3-[(2′-(N-trifluoromethylsulfonylcarboxamido) biphen-4-yl)methyl]pyrido[2,3-d]-pyrimidin-4(3H)-one;
(18) 2-n-Butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrido[3,2-d]pyrimidin-4(3H)-one;
(19) 6-[N-Benzyl-N-n-butyloxycarbonyl]amino-2-propyl-3-[(2′-(tetrazol-5-yl))biphen-4-yl) methyl]-pyrido[2, 3-d]pyrimidin-4(3H)-one;
(20) 2-n-Butyl-6-(N-methyl-N-isobutyloxycarbonyl) amino-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl] pyrido[3, 2-d]pyrimidin-4(3H)-one;
(21) 6-(N-Benzyl-N-butanoyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[3,2-d] pyrimidin-4(3H)-one;
(22) 6-(N-Benzoyl-N-n-pentyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[3,2-d] pyrimidin-4(3H)-one;
(23) 6-(N-(p-Chloro)benzoyl-N-n-pentyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl] pyrido[3, 2-d]pyrimidin-4(3H)-one;
(24) 6-(N-(p-Chloro)benzoyl-N-isobutyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl] pyrido[3, 2-d]pyrimidin-4(3H)-one;
(25) 6-(N-n-Propyl-N-isobutyloxycarbonyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl] pyrido [3,2-d]pyrimidin-4(3H)-one;
(26) 6-(N-Benzoyl-N-n-pentyl)amino-3-[2′-(N-benzoylsulfonamido)biphen-4-yl)methyl]-2-n-propylpyrido [3,2-d]pyrimidin-4(3H)-one;
(27) 2-n-Butyl-6-(N-methyl-N-isobutyloxycarbonyl) amino-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl] pyrido[2, 3-d]pyrimidin-4(3H)-one;
(28) 6-(N-Benzyl-N-butanoyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d] pyrimidin-4(3H)-one;
(29) 6-(N-(p-Chloro)benzoyl-N-n-pentyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl] pyrido[2, 3-d]pyrimidin-4(3H)-one;
(30) 6-(N-n-Propyl-N-isobutyloxycarbonyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl] pyrido[2,3-d]pyrimidin-4(3H)-one; and
(31) 6-(N-Benzoyl-N-n-pentyl)amino-3-[2′-(N-benzoylsulfonamido)biphen-4-yl)methyl]-2-n-propylpyrido [2,3-d]pyrimidin-4(3H)-one.

In a third embodiment are those compounds of formula (I) wherein:

M is a C atom;

K is C=NR^{22};

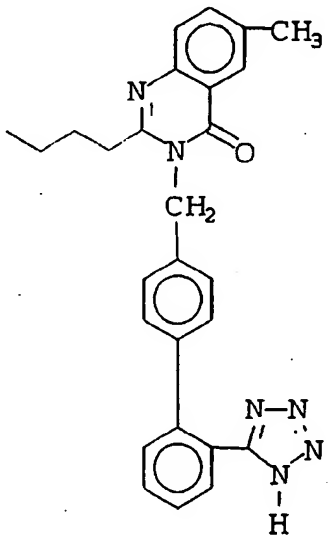
J and L are connected together to form a 6 membered aromatic ring containing one N atom that is not at J and five C atoms which may be substituted at the carbon atoms with R^{7}, R^{8a} and R^{8b}. The class and subclass of this embodiment are the same as those described above.

Exemplifying this subclass are the following compounds:

(1) N-Methyl 2-n-butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]-pyrimidin-4(3H)-imine;
(2) N-Benzyl 2-n-butyl-3-[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]-5-methylpyrido-[3,4-d]pyrimidin-4(3H)-imine;
(3) N-Phenyl-5-amino-2-n-butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]-pyrimidin-4(3H)-imine;
(4) N-Methyl 2-n-butyl-3-[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]-6-isopropylpyrido[3,2-d]-pyrimidin-4(3H)-imine;
(5) N-Butyl 2-n-butyl-3-[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]-5-(N-isopropylcarbamoyl)-aminopyrido[2,3-d]pyrimidin-4(3H)imine;
(6) N-Methyl 2-n-butyl-6-[N-(N-isopropylcarbamoyl)-N-methyl]amino-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pryrido[2,3-d] pyrimidin-4(3H)-imine;
(7) N-Propyl 2-n-butyl-6-[N-(morpholin-4-yl-carbamoyl)-N-methyl]amino-3-[(2′-(tetrazol-5-yl)biphen-4-yl) methyl]pyrido[2,3-d]pyrimidin-4(3H)-imine;
(8) N-Methyl 2-n-butyl-6-(N-isopropyloxycarbonyl-N-methyl)amino-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4(3H)-imine;
(9) N-Benzyl 6-(N-benzyloxycarbonyl-N-methyl) amino-2-n-butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4(3H)-imine;
(10) N-Methyl 3-[(2′-(N-benzoylsulfonamido)biphen-4-yl)methyl]-2-n-butyl-6-(N-isopropyloxy-carbonyl-N-methyl)aminopyrido[2,3-d]pyrimidin-4(3H)-imine; and,

(11) N-Methyl 2-n-butyl-6-(N-isopropyloxycarbonyl-N-methyl)amino-3-[(2'-(N-trifluoromethyl-sulfonyl-carboxamido)biphen-4-yl)methyl]-pyrido[2,3-d]pyrimidin-4(3H)-imine.

In naming compounds of Formula (I) which contain a biphenylmethyl substituent, it should be noted that the following two names for compound (i) shown below are considered to be equivalent:



(i)

(1) 2-n-Butyl-6-methyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4-(3H)-one; or,

(2) 2-n-Butyl-6-methyl-3-[(2'-(tetrazol-5-yl)[1,1']-biphenyl-4-yl)methyl]pyrido[2,3-d]pyrimidin-4(3H)-one.

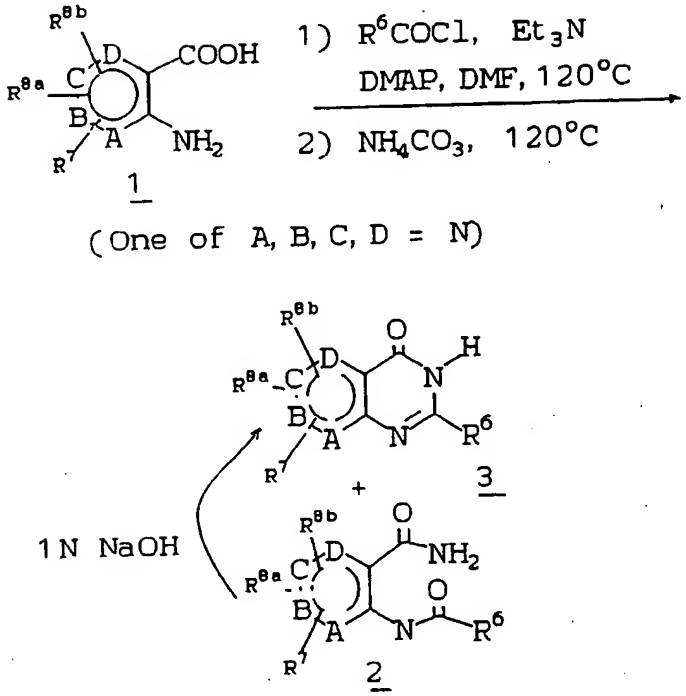
For a general review of the synthesis and reactivity of 2,3-disubstituted pyrido[2,3-d] or [3,4-d] or [3,2-d] or [4,3-d]pyrimidin-4(3H)-ones, see A.R. Katritzky, et al., Comprehensive Heterocyclic Chemistry, Vol. 3, 201 (1984) and W.J. Irwin, et al., Advances in Heterocyclic Chemistry, vol. 10, 149 (1969).

ABBREVIATIONS USED IN SCHEMES

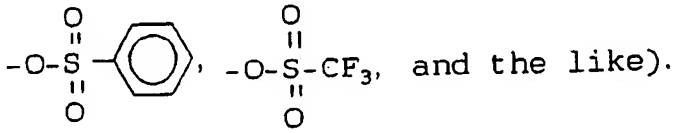
DMAP	Dimethylaminopyridine
-OTs	p-toluenesulphonate
-OTf	Trifluoromethanesulfonate
DMF	Dimethylformamide
DBU	1,8-Diazabicyclo[5.4.0]undecane
FABMS	Fast Atom bombardment mass spectroscopy
THF	Tetrahydrofuran
DMSO	Dimethylsulfoxide
EtAc	Ethyl acetate
HOAc	Acetic Acid
TFA	Trifluoroacetic acid.

Scheme 1 illustrates the preferred preparation of 2-substituted pyrido[2,3-d] or [3,2-d] or [3,4-d] or [4,3-d]pyrimidin-4(3H)-one of formula (I) where E is a single bond. An appropriately substituted ortho amino pyridine carboxylic acid 1 is treated with two equivalents of the requisite acyl chloride in dimethylformamide (DMF) with triethylamine and dimethylaminopyridine (DMAP) at 0°C. This mixture is then heated to 110°C for 2 hours after which time excess ammonium carbonate is added. Any recovered bis amide 2 may be converted to the pyrimidin-4(3H)-one 3 by treatment with base.

SCHEME 1

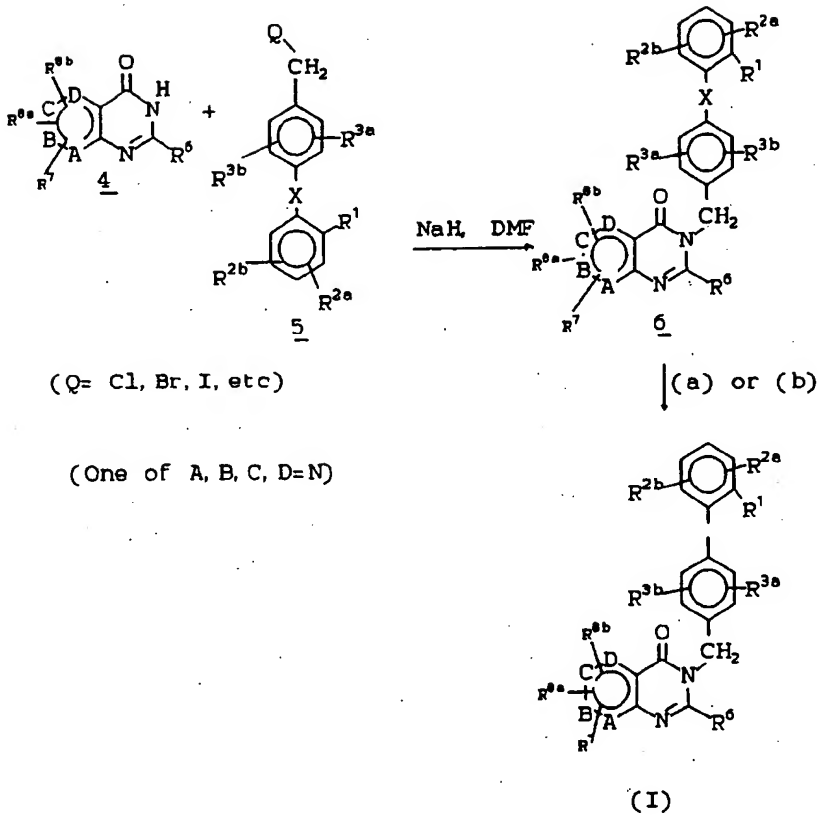


Scheme 2 illustrates the general preparation of 2,3-disubstituted pyrido[2,3-d] or [3,2-d] or [3,4-d] or [4,3-d]pyrimidin-4(3H)-one of Formula I (6) where E is a single bond. An appropriately substituted 2-alkyl-pyrimidin-4(3H)-one 4 is alkylated using sodium hydride and the appropriate alkyl halide 5 (or pseudo halide; i.e, Q is an appropriate leaving group such as



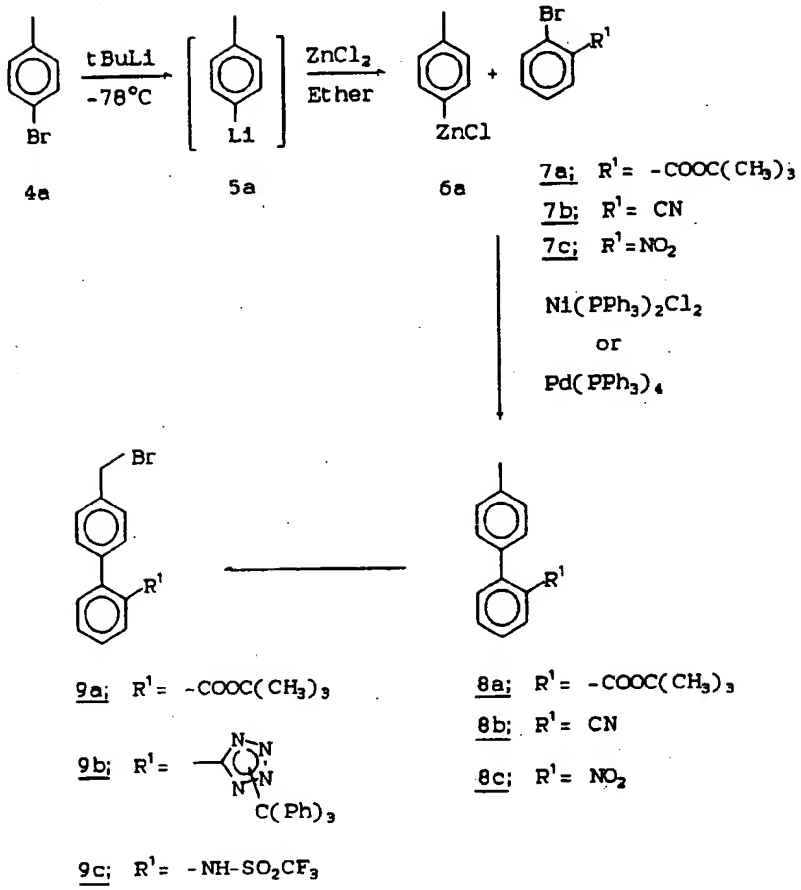
The alkylated material 6 may be transformed into the desired compound of Formula (I) by deprotection of the protecting groups for R^1 or by chemical transformation into the R^1 group desired. For example, when R^1 is a carboxy t-butyl ester or N-triphenylmethyl tetrazole, treatment of 6 with HCl/MeOH or acetic acid will give the desired R^1 carboxy or tetrazolyl functional group. When R^1 in 6 is nitrile, heating with trimethyltin azide will give the tetrazole function.

SCHEME 2



(a) when R^1 is t-butyl or triphenylmethyl treated with acetic acid or HCl/MeOH
(b) when R^1 is C≡N treated with $(CH_3)_3SnN_3$.

REACTION SCHEME 3



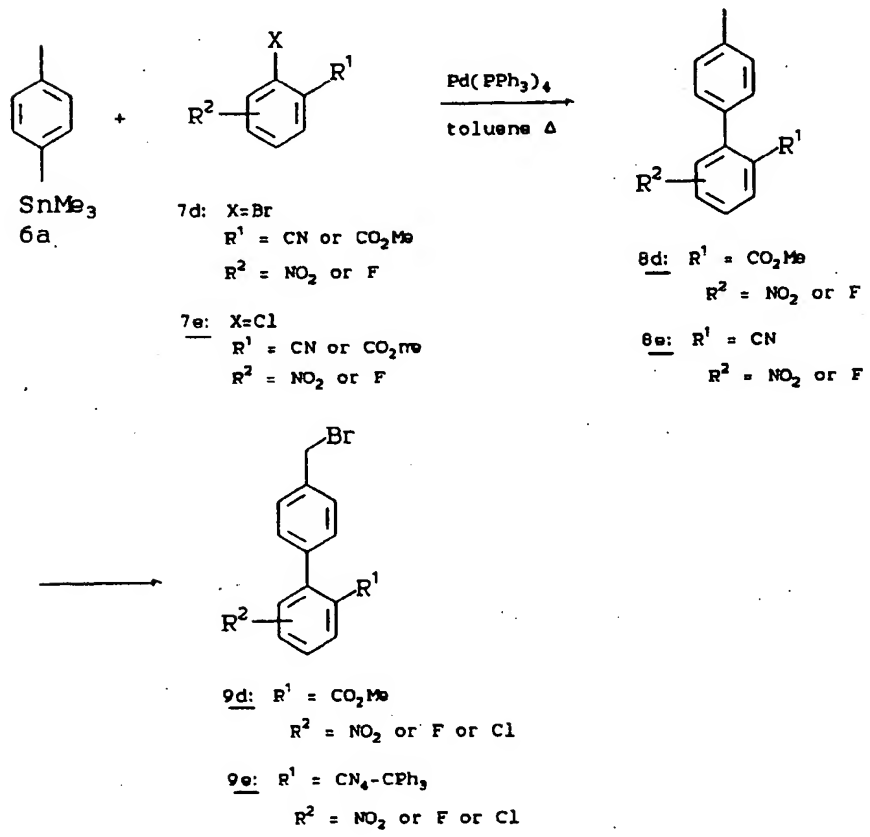
The benzyl halides (5) including the more preferred alkylating agents (9a and 9b, Reaction Scheme 3) can be prepared as described in European Patent Applications 253,310 and 291,969 and the references cited therein. However, a preferred method to prepare the biphenyl precursors 8a, 8b and 8c using Ni(O) or Pd(O) catalyzed cross-coupling reaction [E. Negishi, T. Takahashi, and A. O. King, Org. Synthesis., 66, 67 (1987)] is outlined in Reaction Scheme 3. As shown in Reaction Scheme 3, treatment of 4-bromotoluene (4a) with t-BuLi, followed by the addition of a solution of $ZnCl_2$, produces the organo-zinc compound (6a). Compound (6a) is then coupled with 7a or 7b in the presence of $Ni(PPh_3)_2Cl_2$ catalyst to produce the desired biphenyl compound 8a or 8b (PPh_3=triphenylphosphine).

Similarily, 1-iodo-2-nitro-benzene (7c) is coupled with organo-zinc compound 6a in the presence of $Pd(PPh_3)_4$ catalyst [prepared by treating $Cl_2Pd(PPh_3)_2$ with $(i\text{-}Bu)_2AlH$ (2 equiv.)] to give the biphenyl compound 8c. These precursors, 8a, 8b and 8c, are then transformed into halomethylbiphenyl derivatives 9a, 9b and 9c, respectively, according to procedures described in European Patent Applications 253,310 and 291,969.

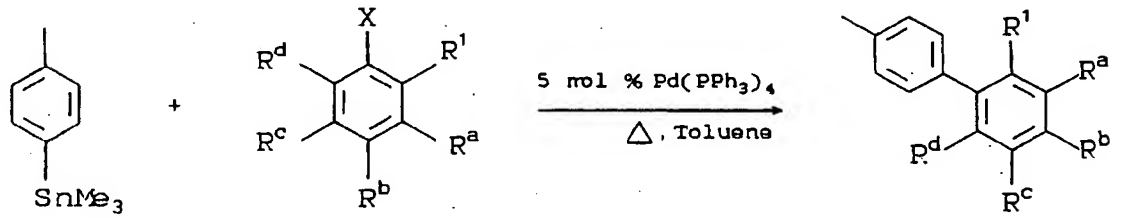
When there is additional substitution on the second phenyl ring (R^{2a}, R^{2b} = hydrogen) the preferred method to prepare the biphenyl precursors 8d and 8e, using the Pd(0) catalyzed cross-coupling reaction [J. K. Stille, Angrew, Chem. Int. Ed. Engl., 25, 508 (1986)], is outlined in reaction Scheme 3a. As shown in reaction Scheme 3a, p-tolyltrimethyltin (6a) is coupled with 7d or 7e in refluxing toluene in the presence of 5 mole % of $Pd(PPh_3)_4$ to produce the desired biphenyl compounds 8d and 8e. Table I illustrates the synthetic utility of this protocol. Compounds 8d ($R^2 = NO_2$) and 8e ($R^2 = NO_2$) could be converted to their respective chlorides by catalytic hydrogenation, diazotization and treatment with copper (I) chloride. The biphenyl fluorides which could not be obtained by direct coupling to a fluoro arylbromide were prepared from 8d ($R^2 = NO_2$) and 8e ($R^2 = NO_2$) via reduction, formation of the diazonium tetrafluoroborate salt and thermal decomposition. These precursors 8d

($R^2 = NO_2$ or F or Cl) and 8e ($R^2 = NO_2$ or F or Cl) are then transformed into the halomethyl biphenyl derivatives 9d and 9e, respectively according to the procedures described in European Patent Applications 253,310 and 292,969.

REACTION SCHEME 3a



Biphenyl Synthesis Table I

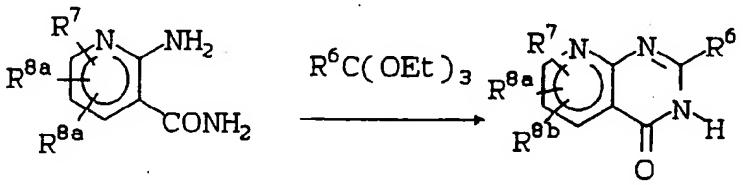


(7d, 7e) (8d, 8e)

X	R^1	R^a	R^b	R^c	R^d	Product (R^a)	Rf (solvent)	Yield
Br	CO_2Me	NO_2	H	H	H	8d (3'-nitro)	0.35(15:1 Hex/EtOAc)	71%
Br	CN	H	NO_2	H	H	8e (4'-nitro)	0.62(2x 6:1 Hex/EtOAc)	74%
Br	CO_2Me	H	F	H	H	8d (4'-fluoro)	0.43(15:1 Hex/EtOAc)	83%
Cl	CO_2Me	H	H	NO_2	H	8d (5'-nitro)	0.22(15:1 Hex/EtOAc)	70%
Br	CO_2Me	H	H	H	NO_2	8d (6'-nitro)	0.24(15:1 Hex/EtOAc)	79%
Br	CN	H	F	H	H	8e (4'-fluoro)	0.44(15:1 Hex/EtOAc)	64%
Cl	CN	H	H	F	H	8e (5'-fluoro)	0.40(15:1 Hex/EtOAc)	62%

Scheme 4 illustrates an alternative method of preparing 2-substituted pyrido[2,3-d] pyrimidin-4-(3H)-one [A. Dornow, et al, Chem. Ber. 98, 1505 (1965); D.M. Mulrey, et al, J. Org. Chem., 29, 2903 (1964); and, S.G. Cottis, et al, J. Org. Chem., 26, 79 (1961)]. An appropriately substituted 2-aminonicotinic acid amide 10 (prepared by partial hydrolysis of the corresponding nitrile) when treated with an alkyl ortho ester gives the corresponding 2-substituted pyrido[2,3-d]pyrimidin-4(3H)-one 11. This conversion could be applied to other isomeric pyridines.

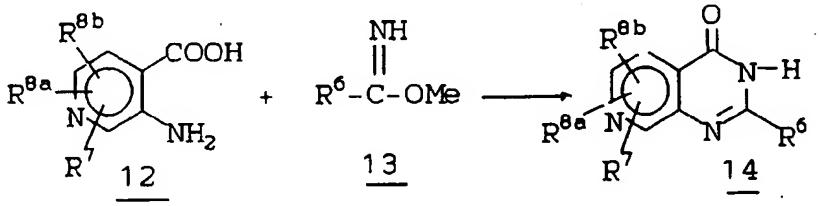
SCHEME 4



10 11

Scheme 5 illustrates an alternative method of preparing 2-substituted pyrido[3,4-d]pyrimidin-4(3H)-ones. An appropriately substituted 3-aminoisonicotinic acid 12 may be reacted with an alkyl imidate ester 13 to give a 2-substituted pyrido [3,4-d]pyrimidin-4(3H)-one 14. [A. deCat, et al, Chem. Abstr., 50, 12063 (1956) and W. Ried, et al, Ann. Chem., 707, 250 (1967)]. This methodology may also be applied to isomeric 2-aminopyridine carboxylic acids.

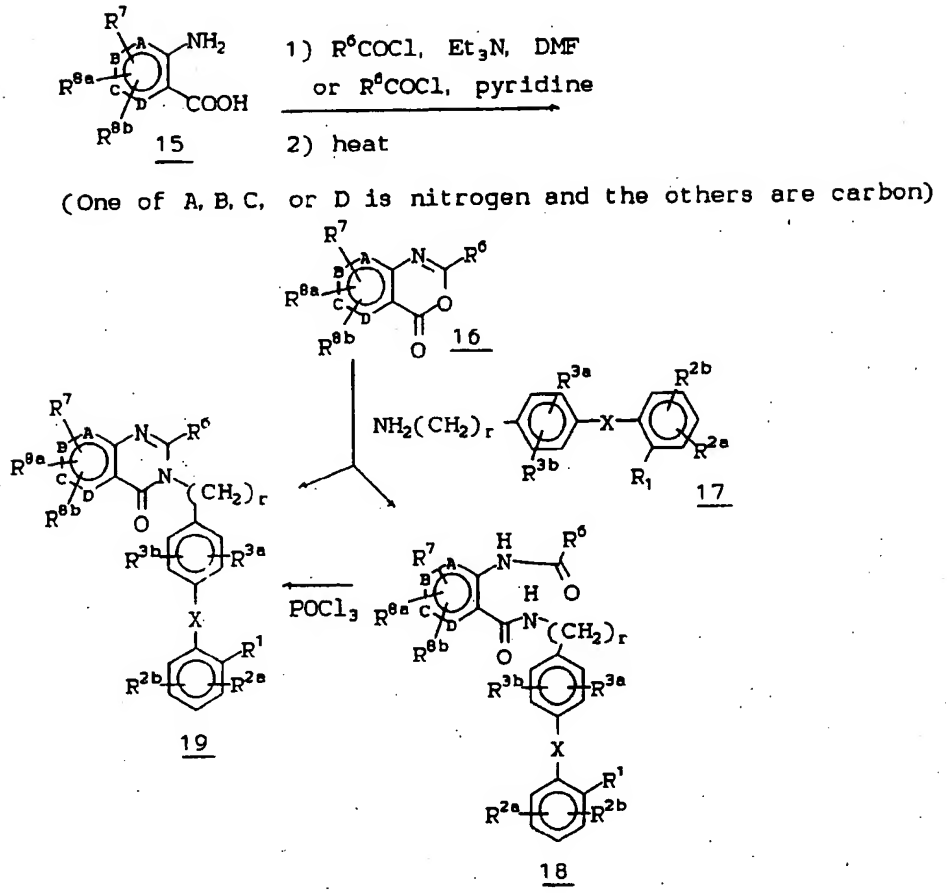
SCHEME 5



12 13 14

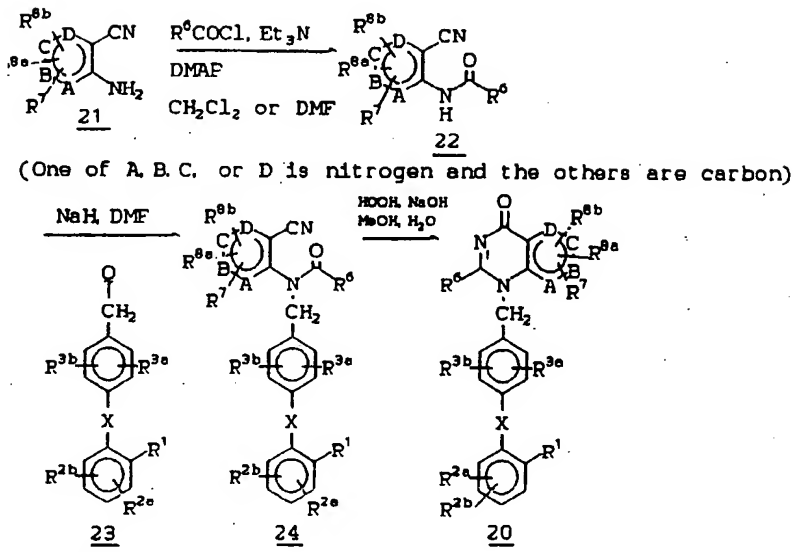
Scheme 6 illustrates a method of preparing 2,3-disubstituted pyrido[2,3-d], [3,2-d], [4,3-d], or [3,4-d]pyrimidin-4(3H)-ones: [A.G. Ismail, et al, J. Chem. Soc., C, 2613 (1967); and W.J. Irwin, et al, J. Chem. Soc., C, 4240 (1965]. An appropriately substituted ortho aminopyridine carboxylic acid 15 when treated with either two equivalents of an acid chloride in pyridine or in the presence of a base such as triethylamine in a solvent such as DMF will give rise on heating to a 2-substituted pyrido[2,3-d] or [3,2-d] or [4,3-d] or [3,4-d][1,3]oxazin-4-ones 16. These may be treated with an alkyl amine 17, and give rise to either the bis amide 18 or the cyclized pyrido-pyrimidin-4(3H)-one 19. The bis amide 18 may in turn be converted to the pyridopyrimidin-4(3H)-one upon dissolution in phosphorus oxychloride.

SCHEME 6



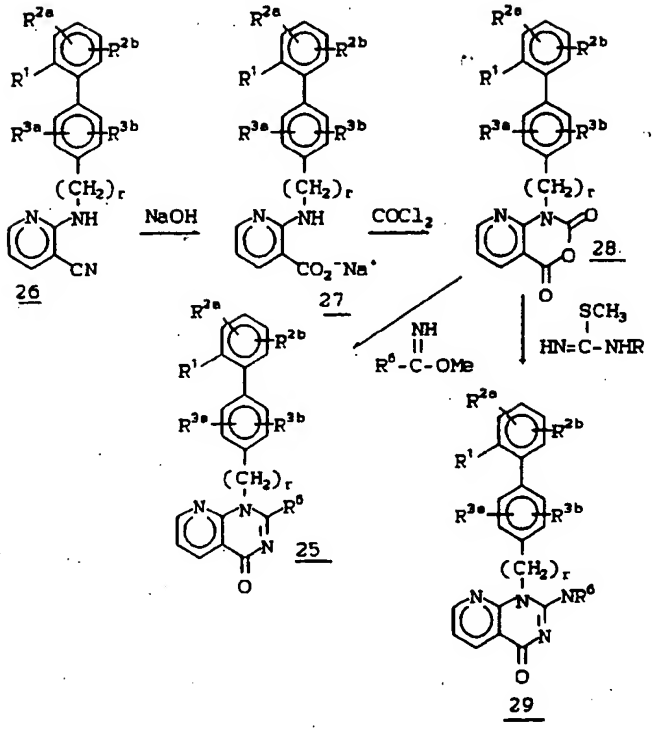
Scheme 7 illustrates the preparation of 1,2-disubstituted pyrido [2,3-d] or [3,2-d] or [3,4-d] or [4,3-d]pyrimdin-4(1H)-ones 20. An appropriately substituted ortho amino pyridine nitrile 21 may be acylated using the requisite acid chloride. The resulting amide 22 may be alkylated with an appropriate alkyl halide (or pseudo halide) 23 in the presence of sodium hydride. The resulting tertiary amide 24 is then rearranged/cyclized with basic hydrogen peroxide.

SCHEME 7



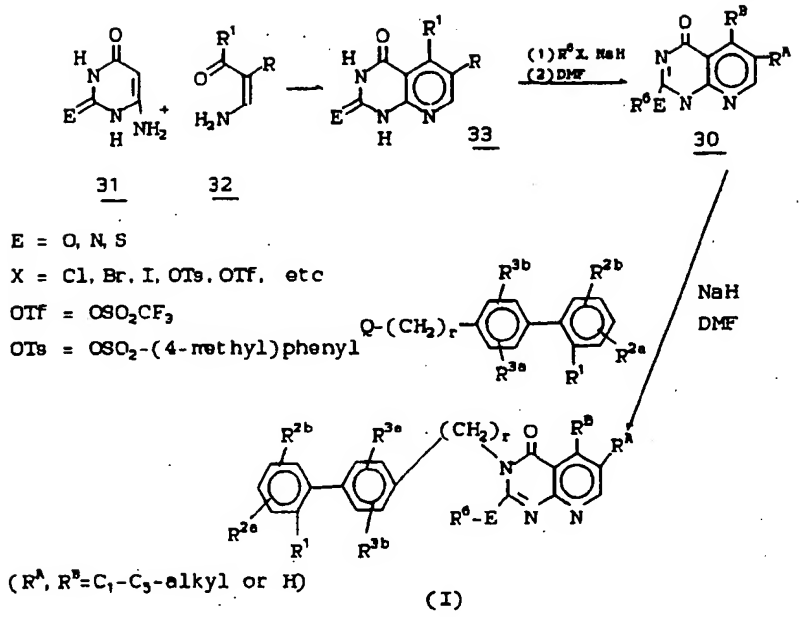
Scheme 8 illustrates a method of preparing 1,2-disubstituted pyrido[2,3-d]pyrimidin-4(1H)-ones 25. An appropriately substituted 2-alkylamino-3-cyanopyridine 26 may be hydrolyzed to the acid salt 27. Reaction with oxalyl chloride will give rise to the isotin 28. Condensation of the isotin with an imidate ester will give the 1,2-disubstituted pyrido [2,3-d]pyrimidin-4(1H)-one 25. [D.G.M., Coppala, et al, J. Het. Chem., 22, 193 (1985)]. Use of a thioamidine will give a 1-alkyl-2-aminoalkylpyrido-[2,3-d]pyrimidin-4(1H)-one 29. This chemistry may be applicable to other isomeric pyridines.

SCHEME 8



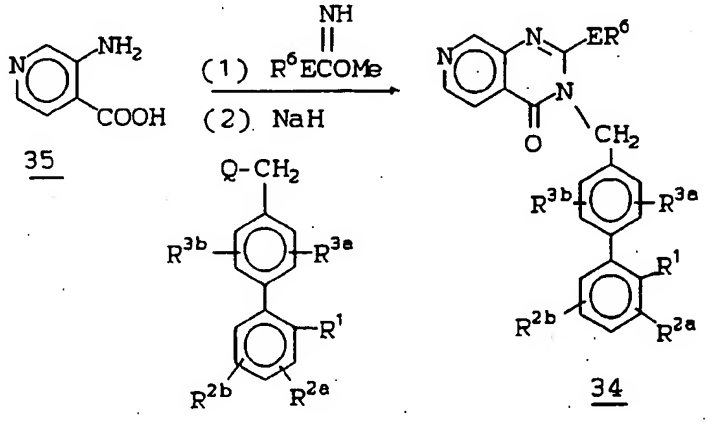
A method of preparing 2,3-disubstituted pyrido[2,3-d]pyrimidin-4(1H)-ones 30 where E=O, S. or N is illustrated in Scheme 9. Condensation of the appropriate pyrimidine-2,3-dione or a derivative thereof 31 with an amino aldehyde 32 gives the pyrido[2,3-d]pyrimidinedione 33. [E. Stark, et al, Tetrahedron, 29, 2209 (1973)]. Alkylation of the heterocycle with an alkyl halide (or pseudohalide) in the presence of sodium hydride gives the 2-substituted pyrido[2,3-d]pyrimidin-4(1H)-one 30. [A. Srinivason, et al, J. Org. Chem., 43, 828 (1978)]. Alkylation of 30 in DMF as described in Scheme 2 gives the desired 2,3-disubstituted pyrido[2,3-d]pyrimidin-4(3H)-one.(I)

SCHEME 9



Scheme 10 describes a method for preparing 2,3-disubstituted pyrido[3,4-d]pyrimidin-4(3H)-ones where E=O, N, S, or C 34 from an ortho aminopyridine carboxylic acid 35 combined with an imidate ester where E=O, N, S, or C. The resulting heterocycle may subsequently be alkylated in the usual fashion to give the desired 2,3-disubstituted pyrido[3,4-d]pyrimidin-4(3H)-one 34.

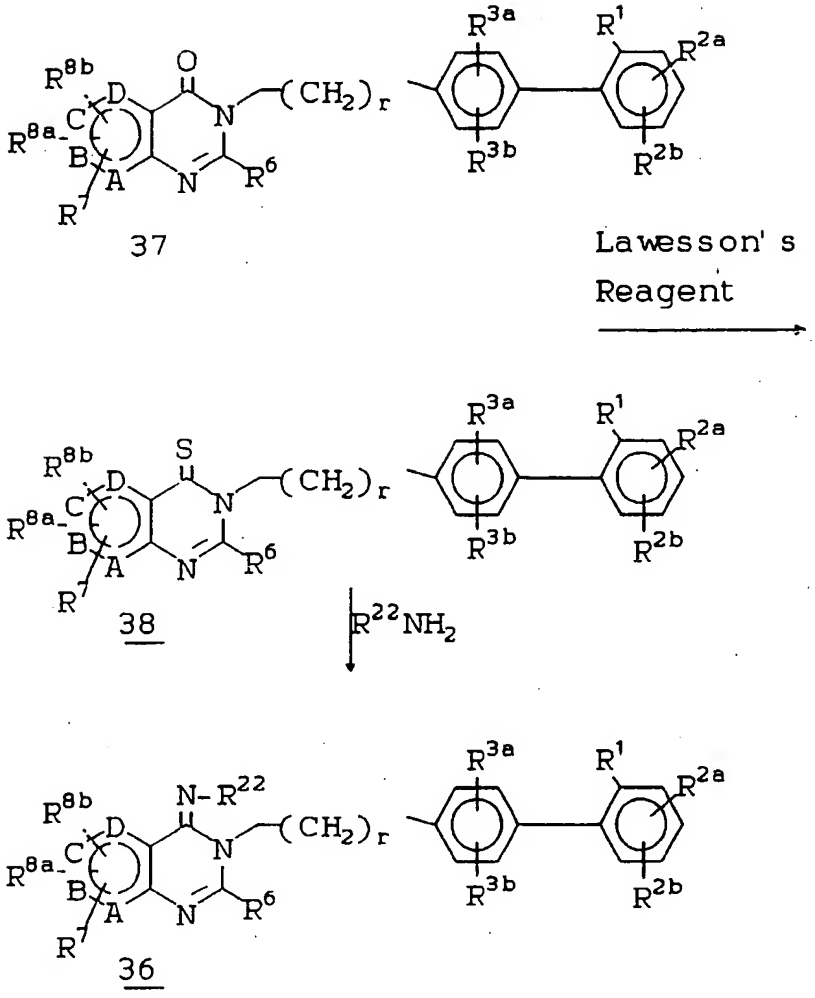
SCHEME 10



Scheme 11 illustrates a method for preparing N-alkyl, 2,3-disubstituted pyrido[4,3-d], or [3,4-d], or [2,3-d], or [3,2-d]pyridin-4(3H)-imines 36.

A suitably protected 2,3-disubstituted pyrido[4,3-d], [3,4-d], [2,3-d] or [3,2-d]pyrimidin-4(3H)-one 37 is treated with Lawesson's Reagent to give the corresponding thione 38. Condensation of the thione with an amine at an elevated temperature in a suitable solvent (e.g., benzene, DMF) gives the desired heterocycle 36 [T. Zimaitg, et al, Indian J. Chem., 15B, 750-751 (1977) and L. Legrand et al, Bull. Chem. Soc. Fr., 1411 (1975)].

SCHEME 11



Note: one of A, B, C, or D is N and the others C.

Compounds of formula I where R^1 is $-CONHSO_2R^{22}$ (where R^{22} = alkyl, aryl or heteroaryl) may be prepared from the corresponding carboxylic acid derivatives (39) as outlined in Scheme 12. The carboxylic acid (39), obtained as described in Scheme 2, can be converted into the corresponding acid chloride by treatment with refluxing thionyl chloride or preferably with oxalyl chloride and a catalytic amount of dimethylformamide at low temperature [A.W. Burgstahler, L.O. Weigel, and C.G. Shaefer-Synthesis, 767, (1976)]. The acid chloride then can be treated with the alkali metal salt of $R^{22}SO_2NH_2$ to form the desired acylsulfonamide (40).

Alternatively, these acylsulfonamides may be prepared from the carboxylic acids using N,N-diphenylcarbamoyl anhydride intermediates [F.J. Brown et al, European Patent Application, EP 199543; K.L. Shepard and W. Halczenko- J. Het. Chem., 16 321 (1979)].

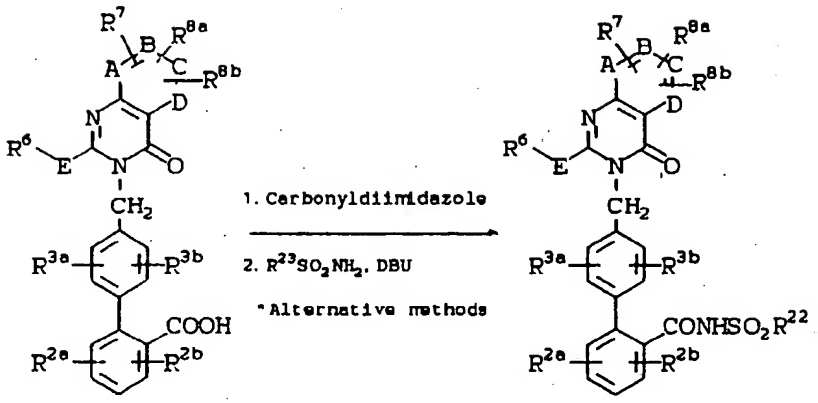
Preferably the carboxylic acids can be converted into acyl-imidazole intermediates, which then can be treated with an appropriate aryl or alkylsulfonamide and diazabicycloundecane (DBU) to give the desired acylsulfonamide 43 [J.T. Drummond and G. Johnson, Tetrahedron. Lett., 29, 1653 (1988)].

Compounds of formula I where R^1 is SO_2NHCOR^{22} may be prepared as outlined in Scheme 13. The nitro compound, for example 8c (prepared as described in Scheme 3), can be reduced to the corresponding amino compound and converted into aromatic diazoniun chloride salt, which then can be reacted with sulfur-dioxide

in the presence of a copper (II) salt to form the corresponding arylsulfonyl chloride 41 [H. Meerwein, G. Dittmar, R. Gollner, K. Hafner, F. Mensch and O. Steifort, Chem. Ber., 90, 841 (1957); A.J. Prinsen and H. Cerfontain, Recueil, 84, 24 (1965); E.E. Gilbert, Synthesis, 3 (1969) and references cited therein]. The sulfonyl chloride can be reacted with ammonia in aqueous solution or in an inert organic solvent [F.H. Bergheim and W. Baker, J. Amer. Chem. Soc., 66, (1944), 1459], or with dry powdered ammonium carbonate, [E.H. Huntress and J.S. Autenrieth, J. Amer. Chem. Soc., 63 (1941), 3446; E.H. Huntress and F.H. Carten, J. Amer. Chem. Soc., 62, (1940), 511] to form the sulfonamide 42. The sulfonamide must then be protected preferably with the triphenylmethyl group by reaction with triphenylmethylchloride and triethylamine to give 43. The benzyl bromide 44 may be prepared from the sulfonamide 43 as outlined in Scheme 16, and then can be reacted with an alkali metal salt of an appropriate heterocyclic compound to form the key sulfonamide 45. The sulfonamide 45 may be also prepared from the aromatic sulfonyl chloride 48 by treatment with ammonia. In addition, 48 may be prepared from the aryl amine 47 as outlined in Scheme 14. The reaction of 48 with appropriate acyl chlorides (or acyl-imidazoles or other acylating agents) may produce the desired acylsulfonamides 46.

The compounds bearing R^1 as $-SO_2NHR^{22}$ (where R^{22} is heteroaryl) may be prepared by reacting the aromatic sulfonyl chloride 48 with appropriate heteroaryl amines as outlined in Scheme 14 to give 49. The sulfonyl chloride 48 may be prepared using similar chemistry to that outlined above. The sulfonyl chloride 48 may be the preferred intermediate for the synthesis of this class of compounds. The aromatic sulfonyl chlorides may also be prepared by reacting the sodium salt of aromatic sulfonic acids with PCl_5 or $POCl_3$ [C.M. Suter, The Organic Chemistry of Sulfur, John Wiley & Sons, 459, (1944)]. The aromatic sulfonic acid precursors may be prepared by chlorosulfonation of the aromatic ring with chlorosulfonic acid [E.H. Huntress and F.H. Carten, J. Amer. Chem. Soc., 62, 511 (1940)].

SCHEME 12



39 40

One of A, B, C, D is N and the others C

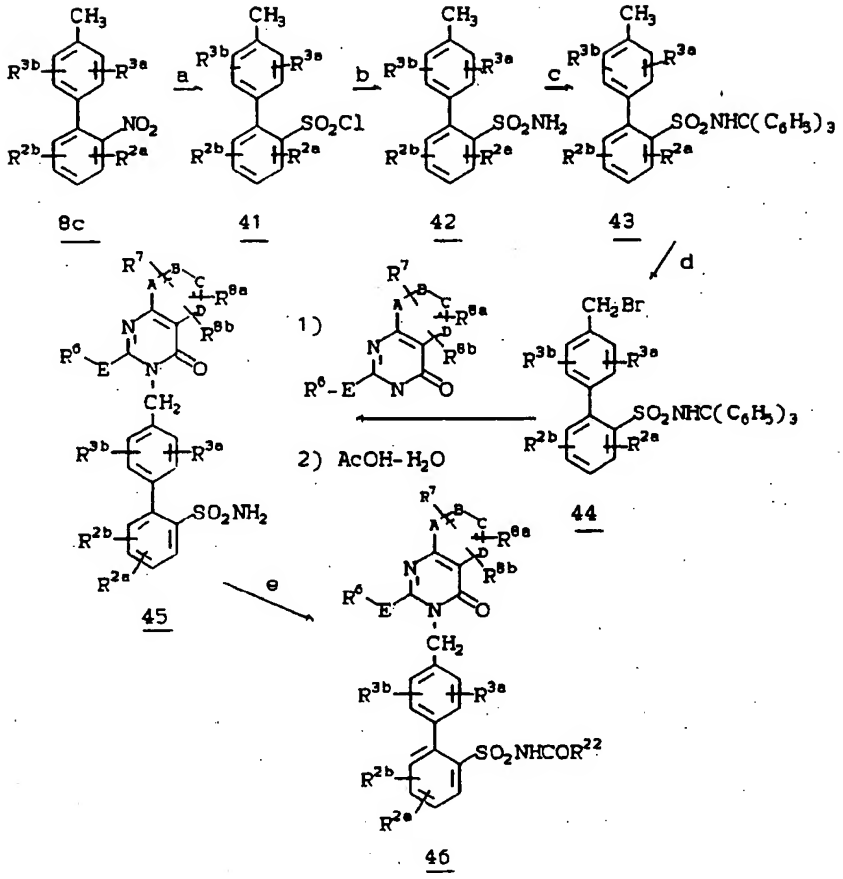
*Alternative Methods:

a) (i) $SOCl_2$, reflux
(ii) $R^{22}SO_2NH^-M^+$ (where M is Na or Li)

b) (i) $(COCl)_2$-DMF, -20°C
(ii) $R^{22}SO_2NH^-M^+$

c) (i) N(N,N-Diphenylcarbamoyl)pyridinium chloride/ Aq. NaOH
(ii) $R^{22}SO_2NH^-M^+$.

SCHEME 13



One of A, B, C, D is N and the others C

SCHEME 13 (CONT'D)

a. (i) H_2/Pd-C,
(ii) $NaNO_2$-HCl,
(iii) SO_2, AcOH, $CuCl_2$

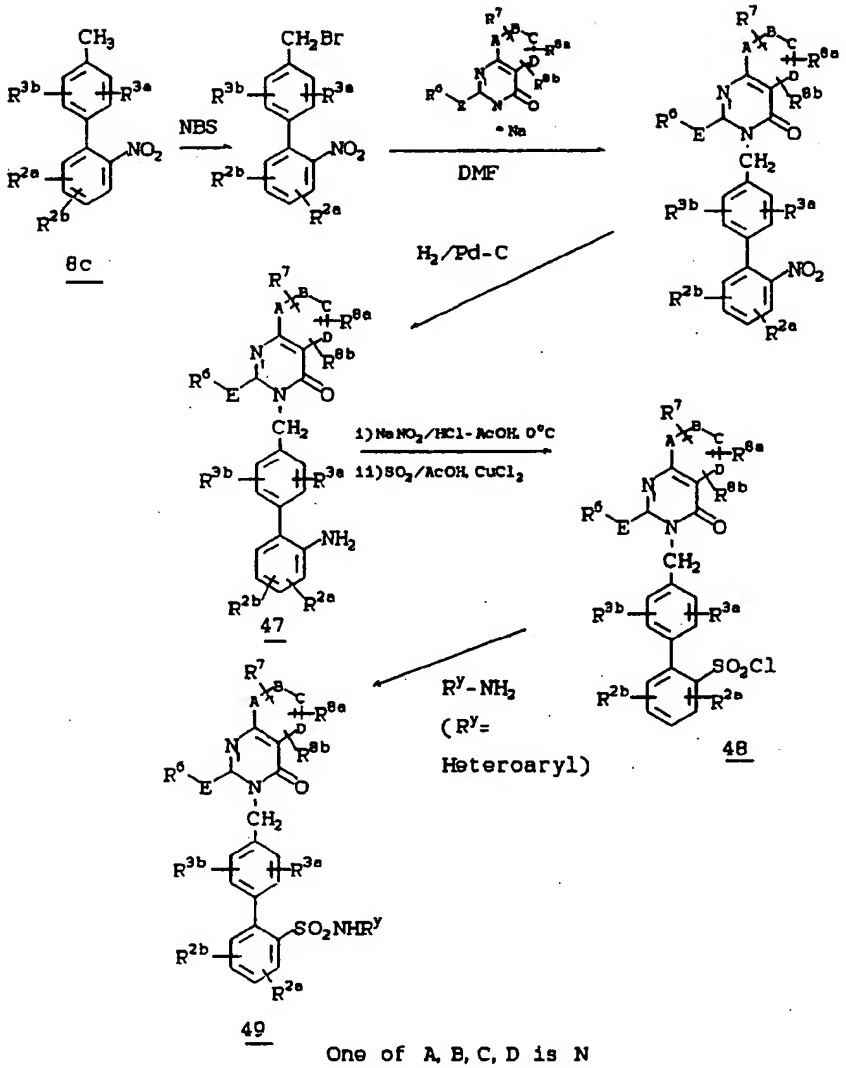
b. NH_3 or $(NH_4)_2CO_3$

c. $(C_6H_5)_3CCl$, Et_3N, CH_2Cl_2, 25°C

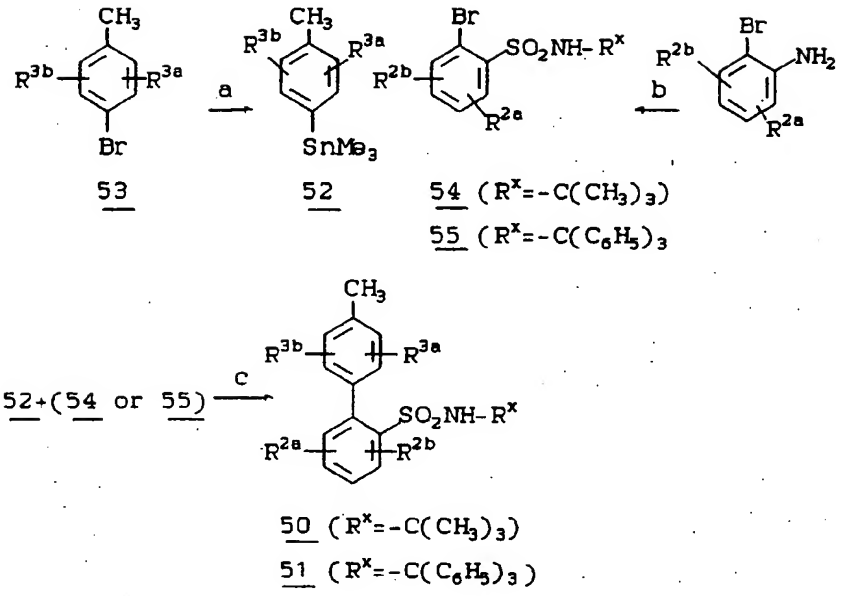
d. N-Bromosuccinimide

e. $R^{22}COCl$ or $R^{22}CO$-Im or other acylating agents.

SCHEME 14


NBS
DMF
H_2/Pd-C
1) $NaNO_2$/HCl-AcOH, 0°C
2) SO_2/AcOH, $CuCl_2$
R^y-NH_2
(R^y= Heteroaryl)
One of A, B, C, D is N
and the others C

SCHEME 15



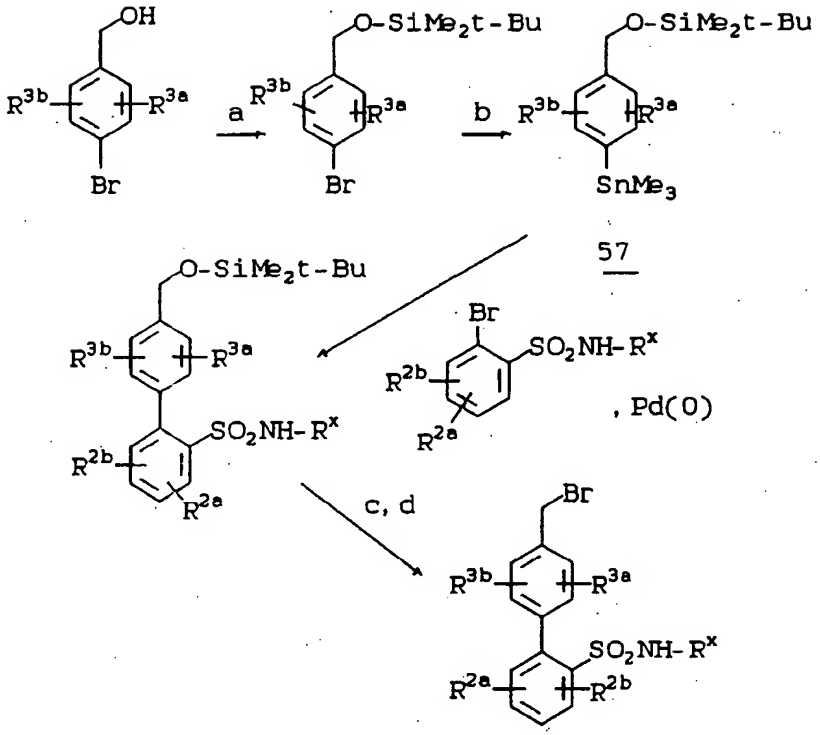
a. (i) t-BuLi/ether, -78°C
(ii) Me_3SnCl

b. (i) $NaNO_2/HCl$
(ii) SO_2, $CuCl_2$

c. $Pd(PPh_3)_4$, Toluene, reflux or $(PPh_3)_2PdCl_2$, DMF, 90°C.

The biaryl sulfonamides 50 and 51 (described in Scheme 13 as 43) can be prepared alternatively using palladium(0) catalyzed cross-coupling reactions of appropriate aryl-organotin precursors [J.K. Stille, Pure Appl. Chem., 57, 1771 (1985); T.R. Baiely, Tetrahedron Lett., 27, 4407 (1986); D.A. Widdowson and Y.Z. Zhang, Tetrahedron, 42, 2111 (1986)], as outlined in Scheme 15. The organotin compound 52 [S.M. Moerlein, J. Organometallic Chem., 319, 29 (1987)], obtained from the aromatic precursor 53, may be coupled with aryl sulfonamide 54 and 55 using $Pd(PPh_3)_4$ or $(PPh_3)_2PdCl_2$ as catalysts to give biaryl sulfonamide 50 and 51. Similarly, the benzyl bromide 56 may be alternatively prepared from the appropriate organotin precursor 57 using the Pd(0) catalyzed cross-coupling reaction as outlined in Scheme 16.

SCHEME 16

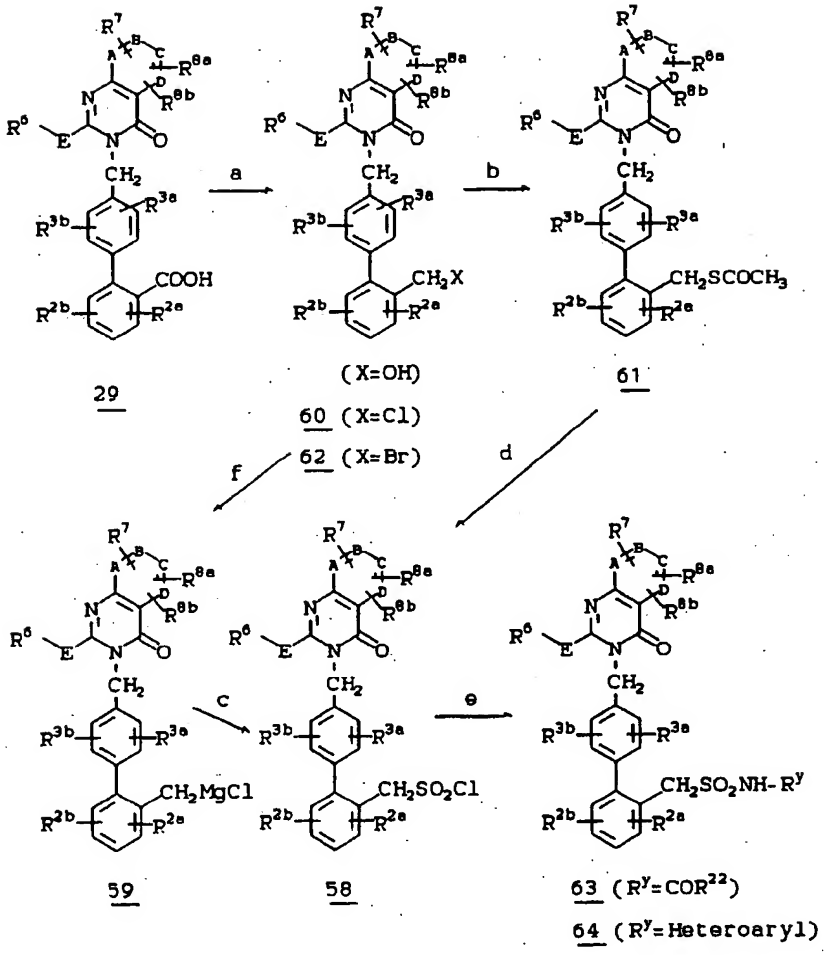


56(a) [R^x=-$C(C_6H_5)_3$]

56(b) [R^x=-$C(CH_3)_3$]

a. t-BuMe_2Si-Cl/Imidazole, DMF
b. t-BuLi, -78°C, Me_3SnCl
c. Tetrabutylammonium fluoride
d. CBr_4/Ph_3P.

SCHEME 17



One of A, B, C, D is N and the others C

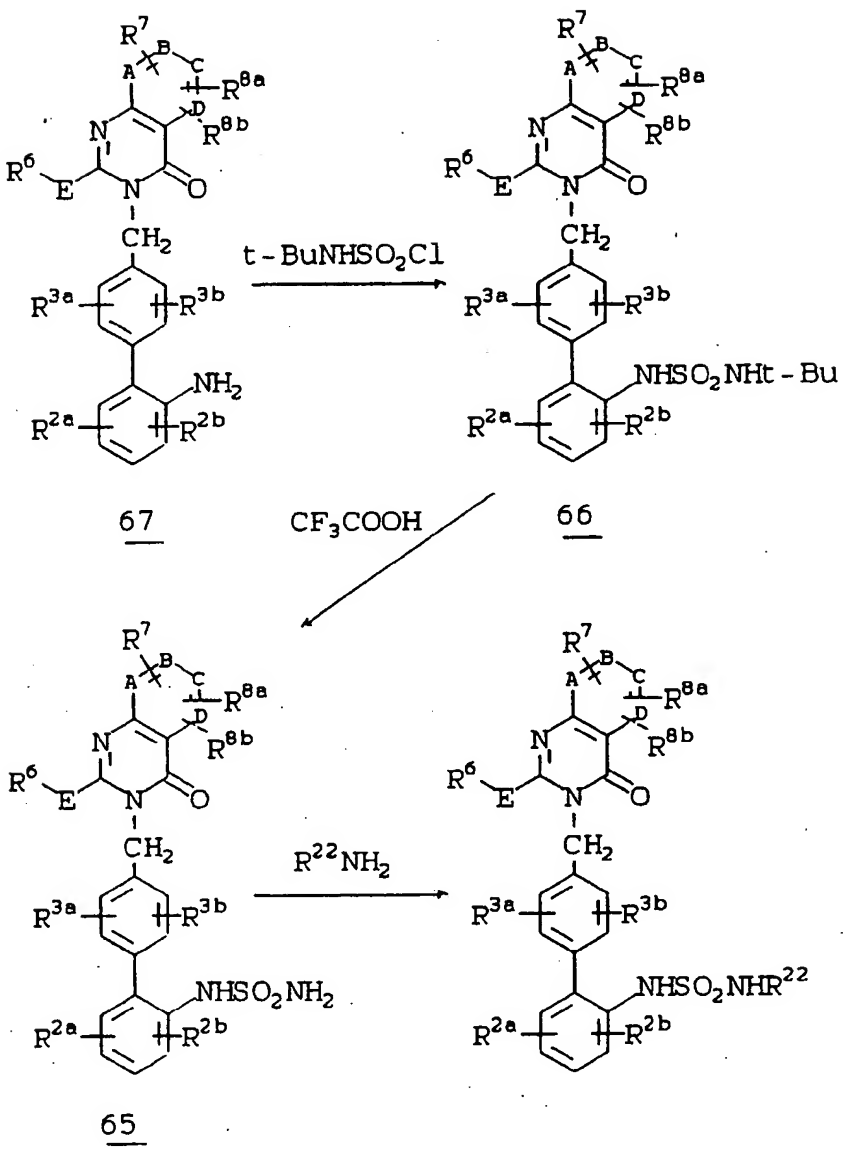
SCHEME 17 (CONT'D)

a. (i) $EtOCOCl/Et_3N$, THF, 0°C
(ii) $NaBH_4$
(iii) CCl_4 or CBr_4/PPh_3
b. AcSK
c. SO_2Cl_2
d. Cl_2, AcOH, H_2O or,
(i) SO_2Cl_2
(ii) oxidation
e. R^yNH_2 or,
(i) NH_3
(ii) Acylation
f. Mg.

The compounds bearing R^1= $-CH_2SO_2NHCOR^{22}$ and $-CH_2SO_2NHR^{22}$ may be prepared as outlined in Scheme 17. The key precursor aryl-methanesulfonyl chloride 58 may be prepared either from the reaction of aryl-methylmagnesium chloride 59, obtained from the corresponding benzyl chloride 60 and magnesium, or by oxidation of the aryl-methylthioacetate 61 (prepared from the benzyl bromide 62 with chlorine in presence of trace amount of water [Bagnay and Dransch, Chem. Ber., 93, 784 (1960)]. Alternatively, the aryl-methylthioacetate 61 can be oxidized with sulfuryl chloride in presence of acetic anhydride to form arylmethylsulfinyl chloride [S. Thea and G. Cevasco, Tet. Lett., 28, 5193 (1987)], which can be further oxidized with appropriate oxidizing agents to give the sulfonyl chloride 58. The compounds 63 and 64 can be obtained by reacting the sulfonyl chloride 58 with appropriate amines.

Compounds where R^1= $-NHSO_2NHR^{22}$ may be prepared by the reaction of appropriate primary amines with the sulfamide 65 [S.D. McDermott and W.J. Spillane, Synthesis, 192 (1983)], as described in Scheme 18. The compound 65 may be obtained from the corresponding N-t-butylsulfamide 66 after treatment with anhydrous trifluoroacetic acid [J.D. Catt and W.L. Matier, J. Org. Chem., 39, 566 (1974)]. The N-t-butylsulfamide 66 may be prepared by the reaction of the aromatic amine 67 (prepared as in Scheme 14) with t-butylsulfamoyl chloride [W.L. Matier, W.T. Comer and D. Deitchman, J. Med. Chem., 15, 538 (1972)].

SCHEME 18

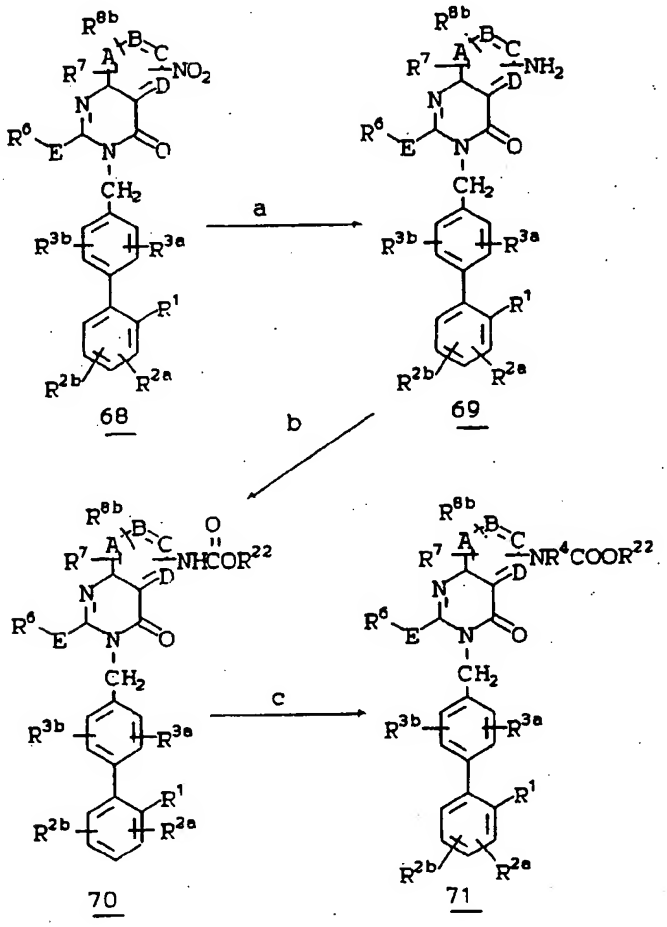


One of A, B, C, or D can be N and the others are C

Further functionalization of compounds of Formula 1 where R^{8a} or R^{8b} is nitro is available through the following route (Scheme 19). The nitro group of 68 may be reduced to the amine 69 by reduction with hydrogen over palladium on carbon. The amine may then be acylated with acid chlorides to give amides under basic conditions. The acylation of the amine with chloroformates is best carried out in the presence of sodium hydride to form the anilinium anion. This anion reacts quickly with chloroformates to give the carbamates 70. The carbamate may be isolated and then deprotonated with lithium hexamethyldisilazide and alkylated to give the N,N-dialkylated carbamates 71. Alternatively this process may be carried out in one pot by first preforming the

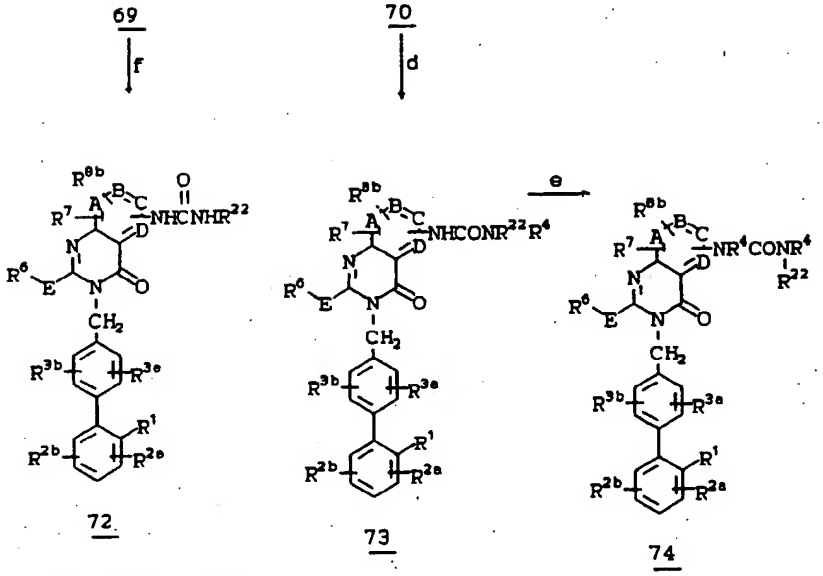
anilinium anion, acylating it and then deprotonating in situ and alkylating with R^4 iodide group to give 71. The amine 69 reacts slowly with isocyanates to give ureas 72. Trisubstituted ureas 73 may be prepared from the benzyl carbamate 70 (R^{22}= benzyl) by treatment with the magnesium salt of a secondary amine. The trisubstituted ureas may be N-alkylated by deprotonation with lithium hexamethyldisilazide and alkylation with an R^4 iodide to give 74. The amine may be further derivatized or converted to other groups by means of chemical procedures well known to those skilled in the art.

SCHEME 19



One of A. B. C or D is N and the others are carbon

SCHEME 19 (CONT'D)



a. H_2, 10%Pd/C, EtAc

b. NaH, $ClCOR^{22}$, DMF

c. $LiN(TMS)_2$, R^4I

d. MeMgBr, R^4NHR^{22}, THF, reflux

e. $LiN(TMS)_2$, R^4I, DMF

f. $R^{22}NCO$, CH_2Cl_2

It will be appreciated by those skilled in the art that the protecting groups used in these syntheses will be chosen to be compatible with subsequent reaction conditions. Ultimately, they will be removed to generate the active compounds of formula (I). For example, R^1 as carboxyl is often protected as its t-butyl ester which in the last step is removed by treatment with trifluoroacetic acid. Aqueous acetic acid employed overnight is a preferred method to remove a trityl protecting group to liberate an R^1 tetrazole group.

The compounds of this invention form salts with various inorganic and organic acids and bases which are also within the scope of the invention. Such salts include ammonium salts, alkai metal salts like sodium and potassium salts, alkaline earth metal salts like the calcium and magnesium salts, salts with organic bases; e.g., dicyclohexylamine salts, N-methyl-D-glucamine, salts with amino acids like arginine, lysine, and the like. Also, salts with organic and inorganic acids may be prepared; e.g., HCl, HBr, H_2SO_4, H_3PO_4, methane-sulfonic, toluensulfonic, maleic, fumaric, camphorsulfonic. The non-toxic, physiologically, acceptable salts are preferred, although other salts are also useful; e.g., in isolating or purifying the product.

The salts can be formed by conventional means such as by reacting the free acid or free base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the cations of an existing salt for another cation on a suitable ion exchange resin.

Angiotensin II (AII) is a powerful arterial vasoconstrictor, and it exerts its action by interacting with specific

receptors present on cell membranes. The compounds described in the present invention act as competitive antagonists of AII at the receptors. In order to identify AII antagonists and determine their efficacy in vitro, the following two ligand-receptor binding assays were established.

Receptor binding assay using rabbit aortae membrane preparation:

Three frozen rabbit aortae (obtained from Pel-Freeze Biologicals) were suspended in 5mM Tris-0.25M Sucrose, pH 7.4 buffer (50 ml) homogenized, and then centifuged. The mixture was filtered through a cheesecloth and the supernatant was centrifuged for 30 minutes at 20,000 rpm at 4°C. The pellet thus obtained was resuspended in 30 ml of 50mM Tris-5 mM $MgCl_2$ buffer containing 0.2% Bovine Serum Albumin and 0.2 mg/ml Bacitracin and the suspension was used for 100 assay tubes. Samples tested for screening were done in duplicate. To the membrane preparation (0.25 ml) there was added ^{125}I-Sar^{1}Ile^8-angiotensin II [obtained from New England Nuclear] (10µl; 20,000 cpm) with or without the test sample and the mixture was incubated at 37°C for 90 minutes. The mixture was then diluted with ice-cold 50mM Tris-0.9% NaCl, pH 7.4 (4ml) and filtered through a glass fiber filter (GF/B Whatman 2.4" diameter). The filter was soaked in scintillation cocktail (10 ml) and counted for radioactivity using Packard 2660 Tricarb liquid scintillation counter. The inhibitory concentration (IC_{50}) of potential AII antagonist which gives 50% displacement of the total specifically bound ^{125}I-Sar^{1}Ile^8-angiotensin II was presented as a measure of the efficacy of such compounds as AII antagonists.

Receptor assay using Bovine adrenal cortex preparation

Bovine adrenal cortex was selected as the source of AII receptor. weighed tissue (0.1 g is needed for 100 assay tubes) was suspended in Tris.HCl (50mM), pH 7.7 buffer and homogenized. The homogenate was centrifuged at 20,000 rpm for 15 minutes. Supernatant was discarded and pellets resuspended in buffer [Na_2HPO_4 (10mM)-NaCl (120mM)-disodium EDTA (5mM) containing phenylmethane sulfonyl fluoride (PMSF)(0.1mM)]. (For screening of compounds, generally duplicates of tubes are used). To the membrane preparation (0.5 ml) there was added 3H-angiotensin II (50mM) (10µl) with or without the test sample and the mixture was incubated at 37°C for 1 hour. The mixture was then diluted with Tris buffer (4ml) and filtered through a glass fiber filter (GF/B whatman 2.4" diameter). The filter was soaked in scintillation cocktail (10ml) and counted for radioactivity using Packard 2660 Tricarb liquid scintillation counter. The inhibitory concentration (IC_{50}) of potential AII antagonist which gives 50% displacement of the total specifically bound ^{3}H-angiotensin II was presented as a measure of the efficacy of such compounds as AII antagonists.

Using the methodology described above, representative compounds of the invention were evaluated and were found to exhibit an activity of at least IC_{50}<50µM thereby demonstrating and confirming the utility of the compounds of the invention as effective AII antagonists.

The potential antihypertensive effects of the compounds described in the present invention may be evaluated using the methodology described below:

Male Charles River Sprague-Dawley rats (300-375 gm) were anesthetized with methohexital (Brevital; 50 mg/kg i.p.) and the trachea was cannulated with PE 205 tubing. A stainless steel pithing rod (1.5 mm thick, 150 mm long) was inserted into the orbit of the right eye and down the spinal column. The rats were immediately placed on a Harvard Rodent Ventilator (rate - 60 strokes per minute, volumn - 1.1 cc per 100 grams body weight). The right carotid artery was ligated, both left and right vagal nerves were cut, and the left carotid artery was cannulated with PE 50 tubing for drug administration, and body temperature was maintained at 37°C by a thermostatically controlled heating pad which received input from a rectal temperature probe. Atropine (1 mg/kg i.v.) was then administered, and 15 minutes later propranolol (1 mg/kg i.v.). Thirty minutes later, antagonists of formula (I) were administered intravenously or orally. Angiotensin II was then typically given at 5, 10, 15, 30, 45 and 60 minute intervals and every half hour thereafter for as long as the test compound showed activity. The change in the mean arterial blood pressure was recorded for each angiotensin II challenge and the percent inhibition of angiotensin II response was calculated.

Thus, the compounds of the invention are useful in treating hypertension. They are also of value in the management of acute and chronic congestive heart failure. These compounds may also be expected to be useful in the treatment of secondary hyperaldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and secondary pulmonary hypertension, renal failure such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, end stage renal disease, renal transplant therapy, and the like, renal vascular hypertension, left ventricular dysfunction, diabetic retinopathy, and in the management of vascular disorders such as migraine, Raynaud's disease, luminal hyperplasia, and to minimize the atherosclerotic process. The application of the compounds of this invention for these and similar disorders will be apparent to those skilled in the art.

The compounds of this invention are also useful to treat elevated intraocular pressure and can be administered to patients in need of such treatment with typical pharmaceutical formulations such as tablets, capsules, injectables and the like as well as topical ocular formulations in the form of solutions, ointments, inserts, gels, and the like. Pharmaceutical formulations prepared to treat intraocular pressure would typically contain about 0.1% to 15% by weight, preferably 0.5% to 2% by weight, of a compound of this invention.

In the management of hypertension and the clinical conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. Although the dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize, the dosage range will generally be about 1 to 1000 mg. per patient per day which can be administered in single or multiple doses. Perferably, the dosage range will be about 2.5 to 250 mg. per patient per day; more preferably about 2.5 to 75 mg. per patient per day.

The compounds of this invention can also be administered in combination with other antihypertensives and/or diuretics and/or angiotensin converting enzyme inhibitors and/or calcium channel blockers. For example, the compounds of this invention can be given in combination with such compounds as amiloride, atenolol, bendroflumethiazide, chlorothalidone, chlorothiazide, clonidine, cryptenamine acetates and cryptenamine tannates, deserpidine, diazoxide, guanethidene sulfate, hydralazine hydrochloride, hydrochlorothiazide, metolazone, metoprolol tartate, methyclothiazide, methyldopa, methyldopate hydrochloride, minoxidil, pargyline hydrochloride, polythiazide, prazosin, propranolol, rauwolfia serpentina, rescinnamine, reserpine, sodium nitroprusside, spironolactone, timolol maleate, trichlormethiazide, trimethophan camsylate, benzthiazide, quinethazone, ticrynafan, triamterene, acetazolamide, aminophylline, cyclothiazide, ethacrynic acid, furosemide, merethoxylline procaine, sodium ethacrynate, captopril, delapril hydrochloride, enalapril, enalaprilat, fosinopril sodium, lisinopril, pentopril, quinapril hydrochloride, ramapril, teprotide, zofenopril calcium, diflusinal, diltiazem, felodipine, nicardipine, nifedipine, niludipine, nimodipine, nisoldipine, nitrendipine, and the like, as well as admixtures and combinations thereof.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly.

To illustrate these combinations, one of the angiotensin II antagonists of this invention effective clinically in the 2.5-250 milligrams per day range can be effectively combined at levels at the 0.5-250 milligrams per day range with the following compounds at the indicated per day dose range: hydrochlorothiazide (15-200 mg) chlorothiazide (125-2000 mg), ethacrynic acid (15-200 mg), amiloride (5-20 mg), furosemide (5-80 mg), propranolol (20-480 mg), timolol maleate (5-60 mg.), methyldopa (65-2000 mg), felodipine (5-60 mg), nifedipine (5-60 mg), and nitrendipine (5-60 mg). In addition, triple drug combinations of hydrochlorothiazide (15-200 mg) plus amiloride (5-20 mg) plus angiotensin II antagonist of this invention (3-200 mg) or hydrochlorothiazide (15-200 mg) plus timolol maleate (5-60) plus an angiotensin II antagonist of this invention (0.5-250 mg) or hydrochlorothiazide (15-200 mg) and nifedipine (5-60 mg) plus an angiotensin II antagonist of this invention (0.5-250 mg) are effective combinations to control blood pressure in hypertensive patients. Naturally, these dose ranges can be adjusted on a unit basis as necessary to permit divided daily dosage and, as noted above, the dose will vary depending on the nature and severity of the disease, weight of patient, special diets and other factors.

Typically, these combinations can be formulated into pharmaceutical compositions as discussed below.

About 1 to 100 mg. of compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which can be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unitform is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occuring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

The following examples illustrate the preparation of the compounds of formula (I) and their incorporation into pharmaceutical compositions and as such are not to be considered as limiting the invention set forth in the claims appended hereto. All ^{1}H-NMR spectra were recorded on a Varian XL-300 Fourier transform spectrometer. Chemical shifts are reported as (parts per million) downfield from tetramethyl silane. Mass spectra were obtained from the Merck and Co. mass spectral facility in Rahway N.J. Analytical TLC was conducted on E.M. Merck precoated silica plates (0.25 mm in glass, Kieselgel 60 F_{254}) with UV visualization. All chromatography was conducted on E. M. Merck silica gel. All reactions were carried out under an atmosphere of dry nitrogen under standard conditions for those skilled in the art.

PREPARATION OF INTERMEDIATES

2-Cyano-4'-methylbiphenyl

To a solution of p-bromotoluene (30 g) in dry ether (150 ml) at -78°C, a solution of t-BuLi in pentane (1.7 M) (210 ml) was added slowly over a period of 1.5 hours, using a dropping funnel. The bath was then removed and the mixture was stirred at room temperature for an additional 2 hours. The contents of the flask were then added slowly (using a cannula) at room temperature to a premixed solution of $ZnCl_2$ in ether (1M) (180 ml) and dry THF (360 ml). The mixture was stirred for 2 hours at that temperature and then the slurry was added (using a cannula) to a solution of 2-bromobenzonitrile (21.3 g) and $NiCl_2(Ph_3P)_2$ (2.1 g) in dry THF (300 ml). The mixture, after stirring at room temperature overnight (18 hours), was poured slowly while stirring into ice-cold IN HCl (1500 ml). The organic layer was separated, and the aqueous phase was extracted with ether (3 x 300 ml). The combined organic layer was washed with water, brine and then dried over $MgSO_4$. Removal of the solvent gave the crude product as a semisolid mass (34 g). The material was purified on a silica-gel flash column eluting with ethylacetate-hexane (1:12) to give the desired nitrile as a low-melting solid (28 g, 88%). NMR ($CDCl_3$): 2.42 (s, 3H), 7.2-7.8 (m, 8H); FAB-MS: m/z 194 (M^++1).

Trimethylstannylazide

To a concentrated solution of NaN_3 (1.2 kg, 18.5 moles) in water (3 L), a solution of trimethyltin chloride (600 g, 3 moles) in dioxane (400 ml) was added in three portions under vigorous stirring. A precipitate formed instantaneously. The mixture, after stirring overnight at room temperature, was filtered. The residue was washed with water, and dried under suction and then in vacuo over P_2O_5. Yield 541 g (88%), mp 120-122°C.

5-[2-(4'-Methylbiphenyl)]tetrazole

To a solution of 2-cyano-4'-methylbiphenyl (390 g, 2.02 moles) in toluene (2.3 L) was added trimethyltin azide (525 g, 2.55 moles) at room temperature. The mixture was refluxed for 24 hours, cooled to room temperature, filtered, washed with toluene and sucked dry in a funnel. The precipitate was resuspended in toluene (3.5 L) and THF (250 ml) was added. Anhydrous HCl was bubbled in at a moderate rate at room temperature to give a clear solution (45 minutes). Addition of HCl gas was continued for another 20 minutes with stirring whereupon a white precipitate formed. The reaction mixture was stirred overnight. The solid product was filtered, washed with toluene followed with ether and then dried under vacuum. This produced 250 g of the tetrazole. (53% yield). m.p. 152-154°C; ^{1}H-NMR ($CDCl_3$): 2.40 (s, 3H), 7.19 (dd, 1H), 7.55 (m, 2H), 8.25 (dd, 1H).

N-Triphenylmethyl-5-[2-(4'-methylbiphenyl)]tetrazole

To a cloudy solution of 250 g (1.06 mole) of 5-[2-(4'-methylbiphenyl)]tetrazole in CH_2Cl_2 (4 L) was added triphenylmethylchloride (310 g, 1.11 mole) at room temperature. The reaction mixture was stirred and triethylamine (190 ml, 138 g, 1.36 mole) was added portionwise. After addition, the mixture was stirred at reflux for 90 minutes. The solution was cooled to room temperature, washed with water (2 x 1 L) and dried over $MgSO_4$, filtered through a silica gel plug and concentrated on the rotovap to a solid. This was crystallized from toluene to give the product as an off-white solid (425 g, 84%); m.p. 166-168°C; ^{1}H-NMR ($CDCl_3$): 2.28 (s, 3H), 6.9-7.05 (m, 10H), 7.2-7.5 (m, 12H), 7.9 (dd, 1H).

N-Triphenylmethyl-5-[2-(4'-bromomethylbiphenyl)]-tetrazole

To a solution of N-triphenylmethyl-5-[2-(4'methylbiphenyl)]tetrazole (425 g, 0.89 moles) in CCl_4 (4.0 L) were added freshly opened N-bromosuccinimide (159 g, 0.89 mole) and dibenzoyl peroxide (22 g, 0,089 moles). The mixture was refluxed for 2 hours, cooled to room temperature and filtered. The filtrate was concentrated in vacuo to give a thick oil. The addition of ether (2.0 L) to this oil resulted in a clear solution which was followed by crystallization, filtration gave a white solid (367 g, 74%). m.p. 137-139.5°C; ^{1}H-NMR ($CDCl_3$): 4.38 (s, 2H), 6.9-8.0 (m, 23H).

PREPARATION OF 2-ALKYL-PYRIDOPYRIMIDIN-4(1H)-ONES.

EXAMPLE 1

2-n-Butylpyridol[2.3-d]pyrimidin-4(1H)-one.

To a suspension of 3.5 g (25 mmol) of 2-aminonicotinic acid in 15 ml of dry DMF at room temperature was added 7.5 g (75 mmol) of triethyl amine followed by 6.27 g (52 mmol) of valeryl chloride. The mixture was heated to 120°C for 2 hours. TLC (75% EtAc/hexanes) indicated that the starting material had been converted to the less polar bezoxazin. 10.0 g of NH_4CO_3 was added cautiously to the hot reaction mixture. The mixture was cooled and concentrated in vacuo. The residue was taken up in 100 ml of EtAc and 50 ml of water. The phases were separated and the aqueous phase reextracted with 2 x 25 ml EtAc. The combined organic phases were washed with saturated NH_4CO_3 (2 x 25 ml), and brine (1 x 25 ml) and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting with 95:5:0.01 $CHCl_3$:MeOH:NH_4OH to give 0.336 of a tan solid. The solid was dissolved in 6 ml of 0.5M NaOH solution and heated to 100°C for 1 hour. The solution was cooled to room temperature and acidified with 2M HCl to give 0.18 g (0.8 mmol) of a white precipitate. ^{1}H-NMR ($CDCl_3$): 0.97 (t, 3H, J=7.38 Hz), 1.47 (m, 2H), 1.90 (m, 2H), 2.82 (t, 2H, 7.5 Hz), 5.1 (bs, 1H), 7.43 (dd, 1H, J=4.4, 7.8 Hz), 8.58 (dd, 1H, J=1.8, 7.8 Hz), 9.01 (m, 1H).

EXAMPLE 2

2-n-Butylpyrido[3,2-d]pyrimidin-4(1H)-one.

Same procedure as in Example 1 above with 1.5 g (11.7 mmol) of 3-aminopyridine-2-carboxylic acid. The crude product was recrystallized from EtAc/hexane to give 0.79 g (3.89 mmol) of a pale yellow solid, 33% yield. ^{1}H-NMR ($CDCl_3$): 0.94 (t, 3H, J=7.33 Hz), 1.45 (m, 2H), 1.84 (m, 2H), 2.89 (t, 2H, J=7.5 Hz), 7.67 (dd, 1H, J=4.29, 8.36 Hz), 8.04 (d, 1H, J=7.05 Hz), 8.84 (d, 1H, J=3.04 Hz), 12.38 (bs, 1H).

EXAMPLE 3

2-n-Butylpyrido[3.4-d]pyrimidin-4(1H)-one.

Same procedure as in Example 1 above with 10 g (7.2 mmol) of 3-amino-pyridine-4-carboxylic acid. Treatment of the intermediate bis amide with sodium hydroxide followed by acidification to pH 4-5 gave 0.39 g (1.9 mmol) of a pale yellow solid, 26% yield. ^{1}H-NMR (CD_3OD): 0.89 (t, 3H, J=7.3 Hz), 1.47 (m, 2H), 1.72 (m, 2H), 2.61 (t, 2H, J=7.6 Hz), 7.93 (d, 1H, J=5.1 Hz), 8.49 (d, 1H, J=5.1 Hz), 8.87 (s, 1H).

PREPARATION OF 2.3-DIALKYL-PYRIDOPYRIMIDIN-4(3H)-ONES.

EXAMPLE 4

2-n-Butyl-3-(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methylpyrido[2.3-d]pyrimidin-4(3H)-one.

To a suspension of 16.5 mg (0.55 mmol) of 80% NaH in oil in 0.5 ml of dry DMF was added a solution of 0.1 g (5.0 mmol) of 2-butylpyrido[2,3-d]-pyrimidin-4(1H)-one in dry DMF at 0°C. Following the completion of hydrogen evolution, a solution of 0.25 g (0.48 mmol) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphenyl)]tetrazole was added in 0.5 ml of DMF. After stirring overnight at room temperature the reaction mixture was concentrated in vacuo and partitioned between 10 ml water and 10 ml EtAc. The phases were separated and the

aqueous phase reextracted with EtAc (3x5 ml). The combined organic phases were washed with brine (1 x 10 ml) and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo and the residue purified by flash chromatography over silica gel eluting with 40% EtAc/hexanes to give 0.058 g (0.09 mmol) of the product as an oil. ^{1}H-NMR ($CDCl_3$): 0.89 (t, 3H), 1.37 (m, 2H), 1.81 (m, 2H), 2.72 (t, 2H), 5.30 (s, 2H), 6.95-7.0 (m, 8H), 7.12 (d, 2H), 7.20-7.38 (m, 10H), 7.40-7.52 (m, 3H), 7.903 (dd, 1H), 8.63 (dd, 1H), 9.00 (d, 1H).

EXAMPLE 5

2-n-Butyl-3-(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methylpyrido[3.2-d]pyrimidin-4(3H)-one.

To a solution of 0.1 g (0.5 mmol) of 2-n-butylpyrido[3,2-d]pyrimidin-4(1H)-one dissolved in 1 ml of dry DMF at 0°C under N_2 was added 0.5 ml (0.52 mmol) of a 1M solution of lithium hexamethyl disilazane in toluene. The solution was stirred for 30 minutes and then treated with a solution of 0.29 g (0.57 mmol) of N-triphenyl-methyl-5-[2-(4'-bromomethylbiphenyl)]tetrazole dissolved in 1 ml of dry DMF. The solution was warmed to room temperature, stirred overnight and concentrated in vacuo. The residue was partitioned between 10 ml of EtAc and 10 ml of water. The phases were separated and the aqueous phase was extracted with EtAc (3x5 ml). The combined organic extracts were washed with water (2x5 ml) and brine (1x10 ml) and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting with 60% EtAc/hexanes to give 0.169 g (0.24 mmol) of a yellow oil. ^{1}H-NMR ($CDCl_3$): 0.88 (t, 3H, J=7.4Hz), 1.32 (m, 2H), 1.71 (m, 2H), 2.67 (t, 2H, J=7.5Hz), 5.34 (bs, 2H), 6.90 (m, 4H), 7.00 and 7.08 (AB, 4H, J=8.2Hz), 7.21-7.35 (m, 12), 7.45 (m, 2H), 7.67 (dd, 1H, J=4.17, 8.4Hz), 7.93 (m, 1H), 8.00 (d, 1H, J=8.3Hz), 8.86 (dd, 1H, J=1.5, 4.4Hz).

EXAMPLE 6

2-n-Butyl-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methylpyrido[3,4-d]pyrimidin-4(3H)-one.

Alkylation of 0.2 g (1.0 mmol) 2-n-butylpyrido[3,4-d]pyrimidin-4(1H)-one as in Example 4 above, gave after chromatography 0.16 g (0.22 mmol) of a yellow oil. ^{1}H-NMR ($CDCl_3$): 0.91 (t, 3H), 1.32 (m, 2H), 1.71 (m, 2H), 2.69 (t, 2H), 5.30 (bs, 2H), 6.89-6.99 (m, 8H). 7.12 (d, 2H), 7.22-7.35 (m, 10H), 7.47 (m, 2H), 7.92 (dd, 1H), 8.07 (d, 1H), 8.69 (d, 1H), 9.12 (s, 2H).

PREPARATION OF DEPROTECTED 2,3-DIALKYL-PYRIDOPYRIMIDIN-4(3H)-ONES

EXAMPLE 7

2-n-Butyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methylpyrido[2,3-d]pyrimidin-4(3H)-one.

A solution of 0.058 g (0.09 mmol) of 2-n-butyl-3-(2'-(N-triphenylmethyl-tetrazol-5-yl)-biphen-4-yl)methyl-pyrido[2,3-d]pyrimidin-4(3H)-one in a mixture of 0.9 ml acetic acid, 0.3 ml water and 0.3 ml of THF was heated at reflux for 45 minutes. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography over silica gel eluting with 70:30:1 EtAc:hexanes:acetic acid to give 30.4 mg (0.068 mmol) of a glass. ^{1}H-NMR ($CDCl_3$): 0.83 (t, 3H, J=7.3Hz), 1.32 (m, 2H), 1.68 (m, 2H), 2.71 (t, 2H, J=7.8Hz), 5.32 (bs, 2H), 7.01 (s, 8H), 7.32-7.55 (m, 8H), 7.84 (d, 1H, J=7.7Hz), 8.54 (dd, 1H, J=7.8, 1.9Hz), 8.75 (dd, 1H, J=1.9, 4.4Hz), 9.4 (bs, 1H). FABMS: m/z 438 (M^++1).

EXAMPLE 8

2-n-Butyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methylpyrido[3.2-d]pyrimidin-4(3H)-one.

Hydrolysis of 2-n-butyl-3-(2'-(N-triphenyltetrazol-5-yl)biphen-4-yl)methylpyrido[3,2-d]-pyrimidin-4(3H)-one as in Example 7 above, gave the title compound following purification by flash chromatography over silica gel eluting with 50:10:30:1 EtAc:MeOH:hexanes:acetic acid. ^{1}H-NMR (CD_3OD): 0.91 (t, 3H, J=7.3Hz), 1.40 (m, 2H), 1.74 (m, 2H), 2.82 (t, 2H, J=7.8Hz), 5.47 (bs, 2H), 7.0-7.3 (m, 9H), 7.42-7.65 (m, 8H), 7.84 (d, 1H, J=2.1Hz), 8.15 (d, 1H, J=8.1Hz), 8.17 (m, 1H). FABMS: m/z 438 (M^++1).

EXAMPLE 9

2-n-Butyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methylpyrido[3-4-d]pyrimidin-4(3H)-one.

Hydrolysis of 2-n-butyl-3-(2'-(N-triphenyltetrazol-5-yl)biphen-4-yl)methylpyrido[3,4-d]-pyrimidin-4(3H)-one as described in Example 6 gave the title compound following purification by flash chromatography over silica gel eluting with 70:29:1 EtAc:hexanes:acetic acid. ^{1}H-NMR (CD_3OD): 0.82 (t, 3H, J=7.38Hz), 1.33 (m, 2H), 1.69 (m, 2H), 2.71 (t, 2H, J=7.9Hz), 5.37 (bs, 2H), 7.04 (m, 8H), 7.42-7.61 (m, 8H), 7.99 (d, 1H, J=5.4Hz), 8.51 (d, 1H, J=4.5Hz), 8.92 (s, 1H). FABMS: m/z 438 (M^++1).

EXAMPLE 10

Typical Pharmaceutical Compositions Containing a Compound of the Invention

A: Dry Filled Capsules Containing 50 mg of Active Ingredient Per Capsule

Ingredient	Amount per capsule (mg)
2-n-butyl-3-[(2'-tetrazol-5-yl)biphen-4-yl)methyl]pyrido-[2,3-d]pyrimidin-4(3H)-one	50
Lactose	149
Magnesium stearate	1
Capsule (size No. 1)	200

The 2-n-butyl-3-[(2'-tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4(3H)-one can be reduced to a No. 60 powder and the lactose and magnesium stearate can then be passed through a No. 60 blotting cloth onto the powder. The combined ingredients can then be mixed for about 10 minutes and filled into a No. 1 dry gelatin capsule.

B: Tablet

A typical tablet would contain 2-n-butyl-3-[(2'-tetrazol-5-yl)biphen-4-yl)methyl]-pyrido[2,3-d]pyrimidin-4(3H)-one (25 mg), pregelatinized starch USP (82 mg), microcrystalline cellulose (82 mg) and magnesium stearate (1 mg).

C: Combination Tablet

A typical combination tablet would contain, for example, a diuretic such as hydrochlorothiazide and consist of 2-n-butyl-3-[(2'-tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4(3H)-one (50 mg) pregelatinized starch USP (82 mg), microcrystalline cellulose (82 mg) and magnesium stearate (1 mg).

D: Suppository

Typical suppository formulations for rectal administration can contain 2-n-butyl-3-[(2'-tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4(3H)-one (0.08-1.0 mg), disodium calcium edetate (0.25-0.5 mg), and polyethylene glycol (775-1600 mg). Other suppository formulations can be made by substituting, for example, butylated hydroxytoluene (0.04-0.08 mg) for the disodium calcium edetate and a hydrogenated vegetable oil (675-1400 mg) such as Suppocire L, Wecobee FS, Wecobee M, Witepsols, and the like, for the polyethylene

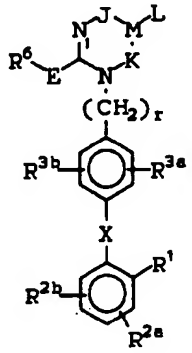
glycol. Further, these suppository formulations can also include another active ingredient such as another antihypertensive and/or a diuretic and/or an angiotensin converting enzyme and/or a calcium channel blocker in pharmaceutically effective amounts as described, for example, in C above.

E: Injection

A typical injectible formulation would contain 2-N-butyl-3-[(2'-tetrazol-5-yl)biphen-4-yl)-methyl]pyrido[2,3-d]pyrimidin-4(3H)-one sodium phosphate dibasic anhydrous (11.4 mg) benzylalcohol (0.01 ml) and water for injection (1.0 ml). Such an injectible formulation can also include a pharmaceutically effective amount of another active ingredient such as another antihypertensive and/or a diuretic and/or an angiotensin converting enzyme inhibitor and/or a calcium channel blocker.

Claims

1. A compound of formula (I):



(I)

wherein

M is a C atom;

L is C or N when connected to K or J to form a ring as defined below;

J is -C(=Y)-where Y is 0 or NR^{21} and K and L are connected together to form a 6 membered aromatic ring containing one N atom that is not at K and five C atoms which may be substituted at the carbon atoms with R^7, R^{8a} and R^{8b};

K is -C(=Y)- where Y is 0 or NR^{21} and J and L are connected together to form a 6 membered aromatic ring containing one N atom that is not at J and five C atoms which may be substituted at the carbon atoms with R^7, R^{8a} and R^{8b} provided that only one of J and K is -C(=Y)-;

R^1 is

(a) $-CO_2R^4$,

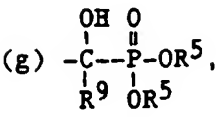
(b) $-SO_3R^5$,

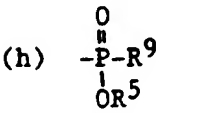
(c) $-NHSO_2CF_3$,

(d) $-PO(OR^5)_2$,

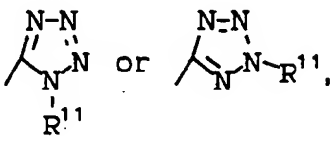
(e) $-SO_2-NH-R^9$,

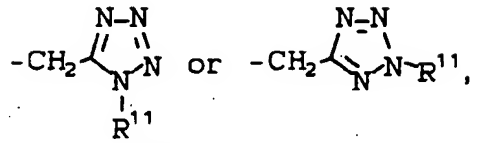
(f) $-CONHOR^5$,

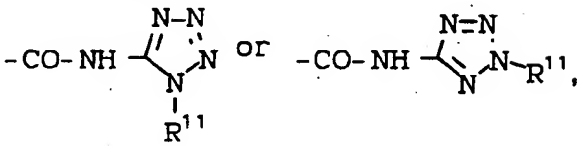
(g)  ,

(h) 

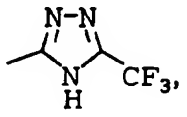
(i) -SO_2NH-heteroaryl as defined below,
(j) -CH_2SO_2NH-heteroaryl as defined below,
(k) -SO_2NH-CO-R^{22},
(l) -CH_2SO_2NH-CO-R^{22},
(m) -CONH-SO_2R^{22},
(n) -CH_2CONH-SO_2R^{22},
(o) -$NHSO_2NHCO$-R^{22},
(p) -$NHCONHSO_2$-R^{22},

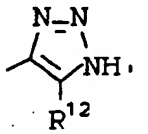
(q)  ,

(r)  ,

(s)  ,

(t) -$CONHNHSO_2CF_3$,
(u) -SO_2NH-CN,

(v)  ,

(w)  ,

(x) -$PO(OR^5)(OR^4)$,
(y) -$SO_2NHCONR^4R^{22}$,

wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted five or six membered aromatic ring which can optionally contain from 1 to 3 heteroatoms selected from the group consisting of O, N or S and wherein the substituents are members selected from the group consisting of -OH, -SH, -C_1-C_4-alkyl, -C_1-C_4-alkoxy, -CF_3, halo (Cl, Br, F, I), -NO_2, -CO_2H, -CO_2-(C_1-C_4-alkyl), -NH_2, -$NH(C_1$-C_4-alkyl) and -$N(C_1$-

C_4-alkyl)$_2$;

R^{2a} and R^{2b} are each independently

(a) H,
(b) halogen, (Cl, Br, I, F)
(c) NO_2,
(d) NH_2,
(e) C_1-C_4-alkylamino,
(f) di(C_1-C_4-alkyl)amino
(g) SO_2NHR^9,
(h) CF_3,
(i) C_1-C_6-alkyl,
(j) C_1-C_6-alkoxy,
(k) C_1-C_6-alkyl-S-,
(l) C_2-C_6-alkenyl,
(m) C_2-C_6-alkynyl;
(n) aryl as defined below,
(o) aryl(C_1-C_4-alkyl),
(p) C_3-C_7-cycloalkyl;

R^{3a} is

(a) H,
(b) halo (Cl, Br, I, F)
(c) C_1-C_6-alkyl,
(d) C_1-C_6-alkoxy,
(e) C_1-C_6-alkoxyalkyl;

R^{3b} is

(a) H,
(b) halo (Cl, Br, I, F)
(c) NO_2,
(d) C_1-C_6-alkyl,
(e) C_1-C_6-acyloxy,
(f) C_3-C_7-cycloalkyl,
(g) C_1-C_6-alkoxy,
(h) -$NHSO_2R^4$,
(i) hydroxy(C_1-C_4-alkyl),
(j) aryl(C_1-C_4-alkyl),
(k) C_1-C_4-alkylthio,
(l) C_1-C_4-alkyl sulfinyl,
(m) C_1-C_4-alkyl sulfonyl,
(n) NH_2,
(o) C_1-C_4-alkylamino,
(p) di(C_1-C_4-alkyl)amino,
(q) fluoro-C_1-C_4-alkyl-,
(r) -SO_2-NHR^9,
(s) aryl as defined below,
(t) furyl,
(u) CF_3,
(v) C_2-C_6-alkenyl,
(w) C_2-C_6-alkynyl;

wherein aryl is phenyl or naphthyl optionally substituted with one or two substituents selected from the group consisting of halogen(Cl, Br, I, F), $N(R^4)_2$, CO_2R^4, C_1-C_4-alkyl, C_1-C_4-alkoxy, NO_2, CF_3, C_1-C_4-alkyl-thio, or OH;

R^4 is H, aryl as defined above or straight chain or branched C_1-C_6 alkyl optionally substituted with aryl or heteroaryl as defined above;

R^{4a} is aryl as defined above or straight chain or branched C_1-C_6-alkyl optionally substituted with aryl as defined above

R^5 is H, $-\overset{R^4}{\underset{|}{C}}H-O-\overset{O}{\overset{||}{C}}-R^{4a}$;

E is a single bond, $-NR^{13}(CH_2)_s-$, $-S(O)_x(CH_2)_s-$where x is 0 to 2 and s is 0 to 5, -CH(OH)-, -O-, CO-;

R^6 is

(a) aryl as defined above optionally substituted with 1 or 2 substituents selected from the group consisting of halo (Cl, Br, I, F) -O-C_1-C_4-alkyl, C_1-C_4-alkyl, $-NO_2$, $-CF_3$, $-SO_2NR^9R^{10}$, -S-C_1-C_4-alkyl, -OH, $-NH_2$, C_3-C_7-cycloalkyl, C_3-C_{10}-alkenyl;

(b) straight chain or branched C_1-C_6-alkyl, C_2-C_5-alkenyl or C_2-C_5-alkynyl each of which can be optionally substituted with a substituent selected from the group consisting of aryl as defined above, C_3-C_7-cycloalkyl, halo (Cl, Br, I, F), CF_3, CF_2CF_3, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-OR^4$ $-N(C_1$-C_4-alkyl)$_2$, $-NHSO_2R^4$, $-COOR^4$, $-SO_2NHR^9$; or

(c) an unsubstituted, monosubstituted or disubstituted heteroaromatic 5 or 6 membered cyclic ring which can contain one to three members selected from the group consisting of N, O, S, and wherein the substituents are members selected from the group consisting of -OH, -SH, C_1-C_4-alkyl, C_1-C_4-alkoxy, $-CF_3$, halo (Cl, Br, I, F), or NO_2;

(d) C_3-C_7-cycloalkyl;

(e) perfluoro-C_1-C_4-alkyl,

(f) H;

R^7 is

(a) H,

(b) straight chain or branched C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

(c) halo(Cl, Br, I, F) or

(d) CF_3; and

R^{8a} and R^{8b} are independently

(a) H,

(b) C_1-C_8-alkyl optionally substituted with a substituent selected from the group consisting of -OH, -guanidino, C_1-C_4-alkoxy, $-N(R^4)_2$, $COOR^4$, $-CON(R^4)_2$, -O-COR^4, -aryl, -heteroaryl, $-S(O)_x-R^{22}$, -tetrazol-5-yl, $-CONHSO_2R^{22}$, $-SO_2NH$-heteroaryl, $-SO_2NHCOR^{22}$, $-PO(OR^4)_2$, $-PO(OR^4)R^9$, $-SO_2NH$-CN, $-NR^{10}COOR^{22}$, $-(CH_2)_{1-4}R^4$,

(c) -CO-aryl,

(d) -C_3-C_7-cycloalkyl,

(e) halo (Cl, Br, I, F),

(f) -OH,

(g) $-OR^{22}$,

(h) -C_1-C_4-perfluoroalkyl,

(i) $-S(O)_x-R^{22}$,

(j) $-COOR^4$,

(k) $-SO_3H$,

(l) $-NR^4R^{22}$,

(m) $-NR^4COR^{22}$,

(n) $-NR^4COOR^{22}$,

(o) $-SO_2NR^4R^9$,

(p) $-NO_2$,

(q) $-N(R^4)SO_2R^{22}$,

(r) $-NR^4CONR^4R^{22}$,

(s) $-O\overset{O}{\overset{||}{C}}NR^{22}R^9$,

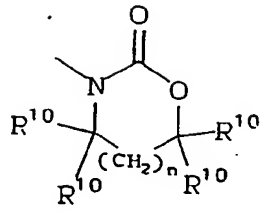
(t) -aryl or -heteroaryl as defined above,

(u) $-NHSO_2CF_3$,

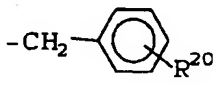
(v) $-SO_2NH$-heteroaryl,

(w) $-SO_2NHCOR^{22}$,

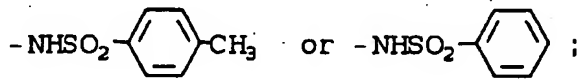
(x) $-CONHSO_2R^{22}$,
(y) $-PO(OR^4)_2$,
(z) $-PO(OR^4)R^4$,
(aa) -tetrazol-5-yl,
(bb) -CONH(tetrazol-5-yl),
(cc) $-COR^4$,
(dd) $-SO_2NHCN$,
(ee) $-NR^4SO_2NR^4R^{22}$,
(ff) $-NR^4SO_2OR^{22}$,
(gg) $-CONR^4R^{22}$,
(hh)



R^9 is H, C_1-C_5-alkyl, aryl or arylmethyl;
R^{10} is H, C_1-C_4-alkyl;
R^{11} is H, C_1-C_8-alkyl, C_1-C_4-alkenyl, C_1-C_4-alkoxy alkyl, or



R^{12} is -CN, $-NO_2$ or $-CO_2R^4$;
R^{13} is H, (C_1-C_4-alkyl)CO-, C_1-C_6-alkyl, allyl, C_3-C_6-cycloalkyl, aryl or arylmethyl;
R^{14} is H, C_1-C_8-alkyl, C_1-C_8-perfluoroalkyl, C_3-C_6-cycloalkyl, aryl or arylmethyl;
R^{15} is H, C_1-C_6-alkyl;
R^{16} is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, aryl or arylmethyl;
R^{17} is $-NR^9R^{10}$, $-OR^{10}$, $-NHCONH_2$, $-NHCSNH_2$,



R^{18} and R^{19} are independently C_1-C_4-alkyl or taken together are $-(CH_2)_q-$ where q is 2 or 3;
R^{20} is H, $-NO_2$, $-NH_2$, -OH or $-OCH_3$;
R^{21} is
(a) aryl as defined above,
(b) heteroaryl as defined above,
(c) C_1-C_4-alkyl optionally substituted with a substituent selected from the group consisting of aryl as defined above, heteroaryl as defined above, -OH, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl)$_2$, $-CO_2R^{4a}$, halo(Cl, Br, F, I), $-CF_3$;
R^{22} is
(a) aryl as defined above,
(b) heteroaryl as defined above,
(c) C_3-C_7-cycloalkyl,
(d) C_1-C_6-alkyl optionally substituted with a substituent selected from the group consisting of aryl as defined above, heteroaryl as defined above, -OH, -SH, C_1-C_4-alkyl, $-O(C_1$-C_4-alkyl), $-S(C_1$-C_4-alkyl), $-CF_3$, halo (Cl, Br, F, I), $-NO_2$, $-CO_2H$, $CO_2-(C_1$-C_4-alkyl), $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl)$_2$, $-PO_3H_2$, $-PO(OH)(O-C_1$-C_4-alkyl), $-PO(OR^4)R^9$;

(e) perfluoro-C_1-C_4-alkyl;

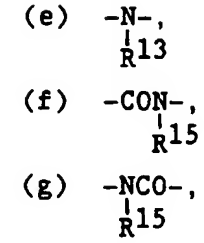
X is

(a) a carbon-carbon single bond,

(b) -CO-,

(c) -O-,

(d) -S-,



(h) $-OCH_2-$,

(i) $-CH_2O-$

(j) $-SCH_2-$,

(k) $-CH_2S-$,

(l) $-NHC(R^9)(R^{10})$,

(m) $-NR^9SO_2-$,

(n) $-SO_2NR^9-$,

(o) $-C(R^9)(R^{10})NH-$,

(p) -CH=CH-,

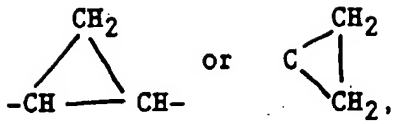
(q) -CF=CF-,

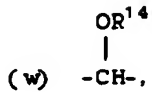
(r) -CH=CF-,

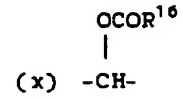
(s) -CF=CH-,

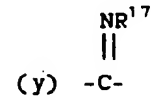
(t) $-CH_2CH_2-$,

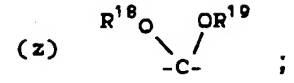
(u) $-CF_2CF_2-$,

(v)  or ,

(w)  ,

(x) 

(y)  , or

(z)  ;

r is 1 or 2; and

the pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 wherein:

M is a C atom;

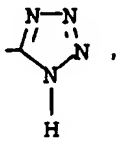
J is -C(O)-;

K and L are connected together to form a 6 membered aromatic ring containing one N atom that is not at K and five C atoms which may be substituted at the carbon atoms with R^7, R^{8a} and R^{8b};

R^1 is

(a) -COOH,

(b)

 ,

(c) $-NH-SO_2CF_3$;

(d) $-SO_2NH$-heteroaryl as defined above,

(e) $-CH_2SO_2NH$-heteroaryl as defined above,

(f) $-SO_2NH-CO-R^{22}$,

(g) $-CH_2SO_2NH-CO-R^{22}$,

(h) $-CONH-SO_2R^{22}$,

(i) $-CH_2CONH-SO_2R^{22}$,

(j) $-NHSO_2NHCO-R^{22}$,

(k) $-NHCONHSO_2-R^{22}$,

R^{2a} is H;
R^{2b} is H, F, Cl, CF_3, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, or aryl;
R^{3a} is H;
R^{3b} is H, F, Cl, CF_3, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_5-C_6-cycloalkyl, $-COOCH_3$, $-CO-OC_2H_5$, $-SO_2-CH_3$, NH_2, $-N(C_1-C_4\text{-alkyl})_2$ or $-NH-SO_2CH_3$;
E is a single bond, -O- or -S-;
R^6 is
(a) C_1-C_5 alkyl optionally substituted with a substituent selected from the group consisting of C_3-C_5-cycloalkyl, Cl, CF_3, CCl_3, $-O-CH_3$, $-OC_2H_5$, $-S-CH_3$, $-S-C_2H_5$, phenyl, or F;
(b) C_2-C_5-alkenyl or C_2-C_5-alkynyl; or,
(c) C_3-C_5-cycloalkyl;
R^7 is H;
R^{8a} and R^{8b} are independently
(a) H,
(b) C_1-C_8-alkyl optionally substituted with $COOR^{4a}$, $OCOR^{4a}$, OH, aryl, or $-(CH_2)_{1-4}R^4$;
(c) OR^{22},
(d) -OH,
(e) $-NO_2$,

(f) $-\overset{\displaystyle R^4}{\underset{|}{N}}-\overset{\displaystyle O}{\overset{\|}{C}}-R^{22}$,

(g) $-CONR^4R^{22}$,

(h) $-NR^4-\overset{\displaystyle O}{\overset{\|}{C}}-O-R^{22}$,

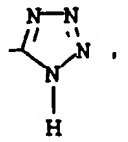
(i) $-NR^4R^{22}$,
(j) halo(Cl, F, Br),
(k) $-CF_3$,
(l) $-CO_2R^{4a}$,
(m) -CO-aryl as defined above,
(n) $-S(O)_x-R^{22}$,
(o) $-SO_2-NR^4R^9$,
(p) $-N(R^4)SO_2R^{22}$,
(q) aryl as defined above,
(r) $-NR^4CONR^4R^{22}$,
(s) $-N(R^4)SO_2N(R^4)R^{22}$;
X is a single bond;
r is one.

3. A compound of Claim 2 selected from the group consisting of:
(1) 2-n-Butyl-1-[(2′-carboxybiphen-4-yl)methyl]pyrido-[2,3-d]pyrimidin-4(1H)-one;
(2) 2-n-Butyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrido[2,3-d]pyrimidin-4-(1H)-one;
(3) 2-n-Butyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl) methyl]pyrido[3,2-d]pyrimidin-4-(1H)-one;
(4) 2-n-Butyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl) methyl]pyrido[3,4-d]pyrimidin-4-(1H)-one;
(5) 2-n-Butyl-1-[(2′-(tetrazol-5-yl)-biphen-4-yl) methyl]pyrido[4,3-d]pyrimidin-4-(1H)-one;
(6) 2-n-Butyl-6-methyl-1-[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4-(1H)-one;
(7) 6-Amino-2-n-butyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4-(1H)-one;
(8) 2-n-Butyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl)-methyl-8-methyl]pyrido[4,3-d]pyrimidin-4-(1H)-one; and ,
(9) 2-n-Butyl-1-5-methyl-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[3,4-d]pyrimidin-4-(1H)-one;
(10) 2-n-Butyl-5,7-dimethyl-1-(2′-(tetrazol-5-yl)-biphen-4-yl)methylpyrido[2,3-d]pyrimidin-4(1H)-one;
(11) 6-Amino-2-n-butyl-5-methyl-1-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4(1H)-one;
(12) 2-n-Butyl-5-methyl-7-methylamino-1-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4(1H)-one;

(13) 1-[(2′-(N-Benzoylsulfonamido)biphen-4-yl)-methyl]-2-n-butyl-5,7-dimethylpyrido[2,3-d]-pyrimidin-4-(1H)-one; and
(14) 2-n-Butyl-5,7-dimethyl-1-[(2′-(N-trifluoromethyl]sulfonylcarboxamido)biphen-4-yl)methyl]-pyrido[2,3-d]pyrimidin-4(1H)-one.

4. A compound of Claim 1 wherein:
M is a C atom;
K is -C(O)-;
J and L are connected together to form a 6 membered aromatic ring containing one N atom that is not at J and five C atoms which may be substituted at the carbon atoms with R^7, R^{8a} and R^{8b};
R^1 is
(a) -COOH,

(b)



(c) $-NH-SO_2CF_3$;
(d) $-SO_2NH$-heteroaryl as defined above,
(e) $-CH_2SO_2NH$-heteroaryl as defined above,
(f) $-SO_2NH-CO-R^{22}$,
(g) $-CH_2SO_2NH-CO-R^{22}$,
(h) $-CONH-SO_2R^{22}$,
(i) $-CH_2CONH-SO_2R^{22}$,
(j) $-NHSO_2NHCO-R^{22}$,
(k) $-NHCONHSO_2-R^{22}$,
R^{2a} is H;
R^{2b} is H, F, Cl, CF_3, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, or aryl;
R^{3a} is H;
R^{3b} is H, F, Cl, CF_3, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_5-C_6-cycloalkyl, $-COOCH_3$, $-CO-OC_2H_5$, $-SO_2-CH_3$, NH_2, $-N(C_1-C_4\text{-alkyl})_2$ or $-NH-SO_2CH_3$;
E is a single bond, -O- or -S-;
R^6 is
(a) C_1-C_6 alkyl optionally substituted with a substituent selected from the group consisting of C_3-C_5-cycloalkyl, Cl, CF_3, CCl_3, $-O-CH_3$, $-OC_2H_5$, $-S-CH_3$, $-S-C_2H_5$, phenyl, or F;
(b) C_2-C_5-alkenyl or C_2-C_5-alkynyl; or,
(c) C_3-C_5-cycloalkyl;
R^7 is H;
R^{8a} and R^{8b} are independently
(a) H,
(b) C_1-C_8-alkyl optionally substituted with $COOR^{4a}$, $OCOR^{4a}$, OH, aryl, or $-(CH_2)_{1-4}R^9$;
(c) $-OR^{22}$,
(d) -OH,

(e) $-\overset{\displaystyle -NO_2}{\underset{\displaystyle R^4O}{|}}$,

(f) $-N(R^4)-\overset{\displaystyle O}{\overset{\|}{C}}-R^{22}$,

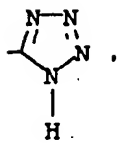
(g) $-CONR^4R^{22}$,

(h) $-NR^4-\overset{O}{\overset{\|}{C}}-O-R^{22}$,

(i) $-NR^4R^{22}$,
(j) halo(Cl, F, Br),
(k) $-CF_3$,
(l) $-CO_2R^{4a}$,
(m) -CO-aryl as defined above,
(n) $-S(O)_x-R^{22}$,
(o) $-SO_2-NR^4R^9$,
(p) $-N(R^4)SO_2R^{22}$,
(q) aryl as defined above,
(r) $-NR^4CONR^4R^{22}$,
(s) $-N(R^4)SO_2N(R^4)R^{22}$;
X is a single bond;
r is one

5. A compound of Claim 4 wherein:
R^1 is
(a) -COOH,

(b)



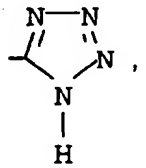
(c) $-NH-SO_2-CF_3$,
(d) $-SO_2NH$-heteroaryl as defined above.
(e) $-SO_2NH-CO-R^{22}$,
(f) $-CONH-SO_2R^{22}$.
E is a single bond;
r is one,
R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H, $-C_1-C_6$-alkyl, $-C_2-C_6$-alkenyl, $-C_2-C_6$-alkynyl, -Cl, -F, $-NO_2$, $-CF_3$;
R^6 is $-C_1-C_4$-alkyl, -cyclopropyl, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CF_3$, $-C_2-C_5$-alkenyl, -cyclopropylmethyl.
R^{8a} and R^{8b} are each independently H, $-C_1-C_4$-alkyl, $-NO_2$, $-NR^4R^{22}$, $-OCH_3$, $-NR^4COOR^{22}$, -Cl, $-CH_2COOR^{4a}$, $-S(O)_x-R^{22}$ -alkyl, $NR^4ONR^4R^{22}$, $CH_2OCO(C_1-C_4$- alkyl), NR^4COR^{22}, CO_2R^{4a}, -F, $-CH_2Ph$, $-CONR^4R^{22}$.

6. A compound of Claim 5 selected from the group consisting of:
(1) 2-n-Butyl-3-[(2′-carboxybiphen-4-yl)-methyl]pyrido[2,3-d]pyrimidin-4(3H)-one;
(2) 2-n-Butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrido[2,3-d]pyrimidin-4(3H)-one;
(3) 2-n-Butyl-3-[(2′-carboxybiphen-4-yl)-methyl]pyrido[3,2-d]pyrimidin-4(3H)-one;
(4) 2-n-Butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrido[4,3-d]pyrimidin-4(3H)-one;
(5) 2-n-Butyl-7-isopropyl-3-[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrido[4,3-d]pyrimidin-4-(3H)-one;
(6) 6-Amino-2-n-Butyl-3-[(2′-(tetrazol-5-yl) biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4-(3H)-one;
(7) 6-Acetamido-2-n-Butyl-3-[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4(3H)-one;
(8) 2-n-Butyl-5-methyl-3-[(2′-(tetrazol-5-yl) biphen-4-yl)methyl]pyrido[3,4-d]pyrimidin-4 (3H)-one;
(9) 2-n-Butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl) methyl-6-thiomethylpyrido[2,3-d]pyrimidin-4(3H)-one;
(10) 2-n-Butyl-7-carboxy-3-[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrido[2,3-d]pyrimidin-4-(3H)-one;
(11) 2-n-Butyl-7-(N-isopropylcarbamoyl)amino-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]-pyrido-[3,2-d] pyrimidin-4-(3H)-one;

(12) 2-n-Butyl-6-(N-isobutyloxycarbonyl)amino-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]-pyrido[2,3-d] pyrimidin-4-(3H)-one;
(13) 2-n-Butyl-6-[N-(morpholin-4-yl)carbamoyl)-N-methyl]amino-3-[(2′-tetrazol-5-yl)biphen-4-yl)-met hyl]pyrido[2,3-d]pyrimidin-4(3H)-one;
(14) 2-n-Butyl-6-(N-isopropyloxycarbonyl-N-methyl)-amino-3-[(2′-tetrazol-5-yl)biphen-4-yl)methyl] pyrido[2,3-d]pyrimidin-4(3H)-one;
(15) 6-(N-Benzyloxycarbonyl-N-methyl)amino-2-n-butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido [2,3-d]pyrimidin-4(3H)-one;
(16) 3-[(2′-(N-Benzoylsulfonamido)biphen-4-yl)]-benzyl-2-n-butyl-6-(N-isopropyloxycarbonyl-N-methy l)aminopyrido[2,3-d]pyrimidin-4(3H)-one;
(17) 2-n-Butyl-6-(N-isopropyloxycarbonyl-N-methyl)amin o-3-[(2′-(N-trifluoromethylsulfonylcarboxamido)biphen-4-yl)methyl]pyrido[2,3-d]-pyrimidin-4(3H)-one;
(18) 2-n-Butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl) methyl]pyrido[3,2-d]pyrimidin-4(3H)-one;
(19) 6-[N-Benzyl-N-n-butyloxycarbonyl]-2-propyl amino-3-[(2′-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrido[2,3-d]pyrimidin-4(3H)-one;
(20) 2-n-Butyl-6-(N-methyl-N-isobutyloxycarbonyl) amino-3-[2′-(tetrazol-5-yl)biphen-4-yl) methyl]pyrido[3,2-d]pyrimidin-4(3H)-one;
(21) 6-(N-Benzyl-N-butanoyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl] pyrido[3,2-d] pyrimidin-4(3H)-one;
(22) 6-(N-Benzoyl-N-n-pentyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl] pyrido[3,2-d] pyrimidin-4(3H)-one;
(23) 6-(N-(p-Chloro)benzoyl-N-n-pentyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl) methyl]pyrido[3,2-d]pyrimidin-4(3H)-one;
(24) 6-(N-(p-Chloro)benzoyl-N-isobutyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl] pyrido[3,2-d]pyrimidin-4(3H)-one;
(25) 6-(N-n-Propyl-N-isobutyloxycarbonyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl) methyl]pyrido[3,2-d]pyrimidin-4(3H)-one;
(26) 6-(N-Benzoyl-N-n-pentyl)amino-3-[2′-(N-benzoyl-sulfonamido)biphen-4-yl)methyl]-2-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one;
(27) 2-n-Butyl-6-(N-methyl-N-isobutyloxycarbonyl) amino-3-[2′-(tetrazol-5-yl)biphen-4-yl) methyl]pyrido[2,3-d]pyrimidin-4(3H)-one;
(28) 6-(N-Benzyl-N-butanoyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl)methyl]pyrido [2,3-d]pyrimidin-4(3H)-one;
(29) 6-(N-(p-Chloro)benzoyl-N-n-pentyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl) methyl]pyrido[2,3-d]pyrimidin-4(3H)-one;
(30) 6-(N-n-Propyl-N-isobutyloxycarbonyl)amino-2-n-propyl-3-[2′-(tetrazol-5-yl)biphen-4-yl) methyl]pyrido[2,3-d]pyrimidin-4(3H)-one; and
(31) 6-(N-Benzoyl-N-n-pentyl)amino-3-[2′-(N-benzoylsulfonamido)biphen-4-yl)methyl]-2-n-propylpyrido[2,3-d]pyrimidin-4(3H)-one.

7. A compound of claim 1 wherein:
M is a C atom;
K is C=NR^{22};
J and L are connected together to form a 6 membered aromatic ring containing one N atom that is not at J and five C atoms which may be substituted at the carbon atoms with R^{7}, R^{8a} and R^{8};
R^{1} is
(a) -COOH,

(b)



(c) -NH-SO_2CF_3;

(d) -SO_2NH-heteroaryl as defined above,
(e) -CH_2SO_2NH-heteroaryl as defined above,
(f) -SO_2NH-CO-R^{22},
(g) -CH_2SO_2NH-CO-R^{22},
(h) -CONH-SO_2R^{22},
(i) -CH_2CONH-SO_2R^{22},
(j) -$NHSO_2NHCO$-R^{22},
(k) -$NHCONHSO_2$-R^{22},
R^{2a} is H;
R^{2b} is H, F, Cl, CF_3, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, or aryl;
R^{3a} is H;
R^{3b} is H, F, Cl, CF_3, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_5-C_6-cycloalkyl, -$COOCH_3$, -CO-OC_2H_5, -SO_2-CH_3, NH_2, -$N(C_1$-C_4-alkyl$)_2$ or -NH-SO_2CH_3;
E is a single bond, -O- or -S-;
R^6 is
(a) C_1-C_5 alkyl optionally substituted with a substituent selected from the group consisting of C_3-C_5-cycloalkyl, Cl, CF_3, CCl_3, -O-CH_3, -OC_2H_5, -S-CH_3, -S-C_2H_5, phenyl, or F;
(b) C_2-C_5-alkenyl or C_2-C_5-alkynyl; or,
(c) C_3-C_5-cycloalkyl;
R^7 is H;
R^{8a} and R^{8b} are independently
(a) H,
(b) C_1-C_8-alkyl optionally substituted with $COOR^{4a}$, $OCOR^{4a}$, OH, aryl, or -$(CH_2)_{1-4}R^4$;
(c) -OR^{22},
(d) -OH,
(e) -NO_2,

(f) $-\overset{R^4}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-R^{22}$,

(g) -CON^4R^{22},

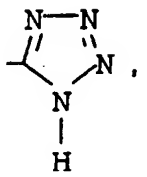
(h) $-NR^4-\overset{O}{\overset{\|}{C}}-O-R^{22}$,

(i) $-NR^4R^{22}$,

(j) halo(Cl, F, Br),
(k) -CF_3,
(l) -CO_2R^{4a},
(m) -CO-aryl as defined above,
(n) -$S(O)_x$-R^{22},
(o) -SO_2-NR^4R^9,
(p) -$N(R^4)SO_2R^{22}$,
(q) aryl as defined above,
(r) -$NR^4CONR^4R^{22}$;
(s) -$N(R^4)SO_2N(R^4)R^{22}$;
X is a single bond;
r is one.

8. A compound of Claim 7 wherein:
R^1 is
(a) -COOH,

(b)



(c) -NH-SO_2-CF_3,
(d) -SO_2NH-heteroaryl as defined above.
(e) -SO_2NH-CO-R^{22},
(f) -CONH-SO_2R^{22}.

E is a single bond;
r is one,
R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H, -C_1-C_6-alkyl, -C_2-C_6-alkenyl, -C_2-C_6-alkynyl, -Cl, -F, -NO_2, -CF_3;
R^6 is -C_1-C_4-alkyl, -cyclopropyl, -$CH_2CH_2CH_2CF_3$, -$CH_2CH_2CF_3$, -C_2-C_6-alkenyl, -cyclopropylmethyl.
R^{8a} and R^{8b} are each independently H, -C_1-C_4-alkyl, -NO_2, -NR^4R^{22}, -OCH_3, -NR^4COOR^{22}, -Cl, -CH_2 $COOR^{4a}$, -$S(O)_x$-R^{22}- alkyl, $NR^4CONR^4R^{22}$, $CH_2OCO(C_1$-C_4- alkyl), NR^4COR^{22}, CO_2R^{4a}, -F, -CH_2Ph, -$CONR^4R^{22}$.

9. A compound of Claim 8 selected from the group consisting of:
(1) Methyl, N-[2-n-butyl-4[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrido[2,3-d]-4(3H)-pyrimidinone imine];
(2) Benzyl, N-[2-n-butyl-3-[(2′-(tetrazol-5-yl)-biphen-4-yl)methyl]-5-methylpyrido[3,4-d] pyrimidin-4 (3H)-imine];
(3) Phenyl-5-amino-N-[2-n-butyl-3-[(2′-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrido-[2,3-d]pyrimidin-4(3H)-imine];
(4) Methyl, N-[2-n-butyl-3-[(2′-(tetrazol-5-yl)-biphen-4-yl)-methyl]-6-isopropylpyrido-[3,2-d]pyrimdin-4 (3H)-imine];
(5) n-Butyl, N-[2-n-butyl-3-[(2′-(tetrazol-5-yl)-biphen-4-yl)-methyl]-5-(N-propylcarbamoyl-amino)pyrido[2,3-d]-4-(3H)-pyrimidinone imine];
(6) Methyl-2-n-butyl-6-[N-(N-isopropylcarbamoyl)-N-methyl]amino-3-(2′-(tetrazol-5-yl)biphen-4-yl)methylpryrido[2,3-d]pyrimidin-4(3H)-imine;
(7) n-Propyl-2-n-butyl-6-[N-(morpholin-4-yl-carbamoyl)-N-methyl]amino-3-(2′(tetrazol-5-yl)biphen-4-yl)methylpyrido[2,3-d]pyrimidin-4(3H)-imine;
(8) Methyl-2-n-butyl-6-(N-isopropyloxycarbonyl-N-methyl)amino-3-(2′-(tetrazol-5-yl)biphen-4-yl)methyl-pyrido(2,3-d]pyrimidin-4(3H)-imine;
(9) Benzyl-6-(N-benzyloxycarbonyl-N-methyl)amino-2-n-butyl-3-(2′-(tetrazol-5-yl)biphen-4-yl)methyl-pyrido[2,3-d]pyrimidin-4(3H)-imine;
(10) Methyl-3-(2′-(N-benzoylsulfonamido)biphen-4-yl)methyl-2-n-butyl-6-(N-isopropyloxycarbonyl-N-methyl)aminopyrido[2,3-d]pyrimidin-4(3H)-imine; and,
(11) Methyl-2-n-butyl-6-(N-isopropyloxycarbonyl-N -methyl)amino-3-(2′-(N-trifluoromethylsulfonyl-carboxamido)biphen-4-yl)methylpyrido[2,3-d]pyrimidin-4(3H)-imine.

10. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of Claim 1.

11. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for the treatment of hypertension.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 30 8791

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 253 310 (DU PONT DE NEMOURS) * page 1, line 13 - line 30; claim 1 *	1,11	C07D471/04 A61K31/505 //(C07D471/04, 239:00,221:00)
A	US-A-4 880 804 (D J CARINI ET AL) * column 1, line 10 - line 28; claim 1 *	1,11	
P,X	EP-A-0 407 342 (CIBA -GEIGY) * page 7, line 11 - line 18; claim 1 *	1,11	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	19 FEBRUARY 1992	HEYWOOD C.J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0601)